MV and TV Repair – Path to Clinical Applications

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Disclosure Statement of Financial Interest

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

Affiliation/Financial Relationship	Company
• Grant/Research Support	• Edwards Lifesciences, Abbott
• Scientific Advisory Board	• Medtronic, Abbott
• Executive Physician Council	• Boston Scientific Corp

Scope of the Problem

TABLE 2. Estimated structural heart disease opportunity: United States

	Patient population	Currently treated
Mitral regurgitation		
Moderate to severe	2,300,000[2,3]	48,000*[2]
Severe	220,000[2,3]	
Aortic stenosis		
All grades	749,000[2,4]	79,000[2]
Severe	125,000†[2,4,5]	
Tricuspid regurgitation		
Moderate to severe	1,600,000‡[2,3]	<8000*[2]

<1% of patients with moderate or severe TR undergoing surgery annually.

Surgery rarely performed (16±5%) 5-years after diagnosis

Stuge O. et al. *Thorac Cardiovasc Surg* 2006; 132: 1258-61

What Evidence do you Need for Valve Therapy Approval and to Change the Guidelines?

Outcome measures: "Hard" clinical endpoints

- US and Europe: Safety
- US: Effectiveness (death, HF hospitalization)

Rigor:	Registries	Small RCT(s)	Large RCT(s)
Approval			
- Europe	✓ (unrestricted)	✓ (unrestricted)	✓ (unrestricted)
- US	✓ (limited)	✓ (limited)	✓ (unrestricted)
Guidelines			
- Europe	IIb	I or IIa	I
- US	IIb	IIa	I

Transcatheter MV Repair: Device Landscape 2017

Edge-to-edge
- MitraClip***
- Pascal*
- MitraFlex

Coronary sinus annuloplasty
- Cardiac Dimensions Carillon**
- Cerclage annuloplasty

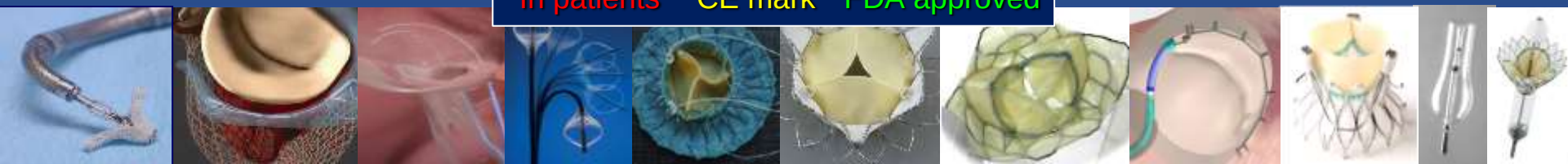
Direct annuloplasty
- Mitralign TAMR**
- Valtech Cardioband**
- GDS Accucinch*
- Millipede IRIS*
- MVRx ARTO*
- Mardil BACE*
- Mitraspan TASRA*
- Valcare Amend*
- Micardia enCor*
- Cardiac Implants RDS
- QuantumCor (RF)
- Valfix

MV replacement
- Edwards CardiAQ*
- Edwards Fortis*
- Neovasc Tiara*
- Abbott Tendyne*
- Medtronic Intrepid*
- HighLife*
- MValve*
- Caisson*
- Cephea
- NCSI NaviGate
- St. Jude
- Micro Interventional
- Valtech CardioValve
- ValveXchange
- MitrAssist
- Braile Quattuor
- Direct Flow
- Sinomed Accufit
- Corona MVR w/Amend ring

MV replacement (cont)
- MitralHeal
- HT Consultant Saturn
- Lutter valve
- Transcatheter Technologies Tresillo
- Venus
- Verso
- Transmural Systems
- 4C

Other approaches
- NeoChord DS 1000**
- Harpoon neochords*
- Babic chords*
- Middle Peak Medical*
- St. Jude leaflet plication*
- Cardiosolutions Mitra-Spacer*
- Mitralix*
- Valtech Vchordal
- Coramaze Mitramaze

*In patients *CE mark *FDA approved



COAPT Principles Adopted by MVARC as a Model for MV Device Trials

Expert consensus document by cardiology valve specialists, HF specialists, interventional cardiologists, mitral surgeons, imaging experts, clinical trialists, statisticians, with participating representatives from FDA

Developed between 2012 - 2014

Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part 1: Clinical Trial Design Principles

A Consensus Document From the Mitral Valve Academic Research Consortium

Gregg W. Stone, MD,*† Alec S. Vahanian, MD,‡ David H. Adams, MD,§ William T. Abraham, MD,‖ Jeffrey S. Borer, MD,¶ Jeroen J. Bax, MD, PhD,# Joachim Schofer, MD,** Donald E. Cutlip, MD,†† Mitchell W. Krucoff, MD,‡‡ Eugene H. Blackstone, MD,§§ Philippe Généreux, MD,*†‖‖ Michael J. Mack, MD,¶¶ Robert J. Siegel, MD,## Paul A. Grayburn, MD,¶¶ Maurice Enriquez-Sarano, MD,*** Patrizio Lancellotti, MD, PhD,††† Gerasimos Filippatos, MD,‡‡‡ Arie Pieter Kappetein, MD, PhD,§§§ for the Mitral Valve Academic Research Consortium (MVARC)

J Am Coll Cardiol 2015;66:278–307
Eur Heart J 2015;36:1851-77

J Am Coll Cardiol 2015;66:308–21
Eur Heart J 2015;36:1878-91

COAPT Trial: Design

~610 patients enrolled at up to 100 sites

Symptomatic HF treated with maximally tolerated guideline directed medical therapy
Significant FMR (≥3+ by echo core lab)
Not appropriate for MV surgery as determined by site's local heart team
Valve anatomy eligible for MitraClip treatment

Randomize 1:1

MitraClip N~305	Control group Standard of care N~305

Clinical and TTE follow-up: Baseline, treatment, 1-week (phone),
1, 6, 12, 18, 24, 36, 48, 60 months

Primary efficacy endpoint: Hospitalization for heart failure within 2 years
Primary safety endpoint: Device-related complications at 1 year

Principal Investigators: Gregg Stone, Michael Mack
Heart Failure Co-Principal Investigators: William Abraham, JoAnn Lindenfeld

Sponsor: Abbott Vascular

COAPT: Enrollment strategies

- Investigator meetings at every major conference; COAPT radio show and webcasts; referral letter program; frequent contact with investigators
- 7 protocol amendments – most including adjustments to the screening process and inclusion/exclusion criteria to make enrollment easier
- Number of sites increased from 75 to 100; added Canada
- Enthusiasm for this landmark trial is extraordinary
- Sponsor is deeply committed….people, $$$

COAPT: Enrollment

Between December 2012 and June 10th, 2017, 600 patients have been randomized at 84 active sites

~0.15 pts/site/month

Enrollment of 610 pts is anticipated to conclude in ~2 weeks,
4.5 years after initiation

COAPT: Enrollment

Between December 2012 and June 10th, 2017, 600 patients have been randomized

10 pts is anticipated conclude in ~2 weeks,

4.5 years after initiation

Our long national nightmare is almost over!

COAPT: Enrollment

Between December 2012 a
June 10th, 2017, 600 p
been randomiz

s is anticipated
ude in ~2 weeks,
4.5 years after initiation

COAPT results in 4th quarter 2018!

MitraClip RCTs in Functional MR (i)

	COAPT	RESHAPE-HF-2
N patients, sites	610 pts @ 100 NA and EU sites	380 pts @ 50 EU sites
Control arm	GDMT ± CRT	GDMT ± CRT
FMR grade	≥3+ (EROA ≥30 mm² and/or Rvol >45 mL by ECL)	≥3+ (EROA ≥30 mm² and/or Rvol >45 mL by ECL)
NYHA class	II, III, or ambulatory IV	III or ambulatory IV
Other inclusion criteria	HF hosp within 12 months or BNP ≥300 pg/ml or nT-proBNP ≥1500 pg/ml within 12 months; MV surgery is not local standard of care	HF hosp within 12 months or BNP ≥350 pg/ml or nT-proBNP ≥1400 pg/ml within 90 days; not eligible for MV surgery
LVEF	≥20% - ≤50%	≥15% - ≤40%
LV volumes	LVESD ≤70 mm	LVEDD ≥55 mm
Primary efficacy endpoint	Recurrent HF hospitalization at 24 months	Death or recurrent HF hospitalization at 12 months
Primary safety	SLDA, device embolizations, endocarditis/MS/device-related complications requiring non-	All-cause mortality, stroke, MI, new renal replacement therapy, non-elective CV

MitraClip RCTs in Functional MR (ii)

	MITRA-FR	MATTERHORN
N patients, sites	288 pts @ 22 French sites	210 pts @ 15 EU sites
Control arm	GDMT ± CRT	MV Surgery
FMR grade	Severe (EROA >20 mm² + Rvol >30 mL) by ECL	≥3+
NYHA class	II - IV	≥III
Other inclusion criteria	HF hosp within 12 months; not eligible for MV surgery	-
LVEF	≥15% - ≤40%	≥20% - ≤45%
LV volumes	-	-
Primary efficacy endpoint	Death or recurrent HF hospitalization at 12 months	Death, HF rehosp, reintervention, assist device implantation or stroke at 12 months
Primary safety endpoint	-	Major adverse events at 30 days
Total follow-up	2 years	1 year
PIs	JF Obadia	J Hausleiter

MitraClip RCTs in Functional MR

- 4 trials randomizing ~1488 patients with heart failure and secondary (functional) MR to MitraClip vs. GDMT or MV Surgery
- As of June 10th, 2017, ~1159 patients have been randomized:

- COAPT – 600/610 (98%) – ~2 more weeks!
- MITRA-FR – 288/288 (100%) – enrolled!
- RESHAPE-HF-2 – 222/380 (58%)
- MATTERHORN – 49/210 (23%)

COAPT Roll-in Results, Adjudicated (n=51)

	30 Days	1 Year
Death	0% (0/51)	16.0% (8/50)
HF hospitalization	11.8% (6/51)	28.0% (14/50)
Stroke	0% (0/51)	2.0% (1/50)
NYHA ⇓ ≥1 class	56.0% (28/50)	60.5% (23/38)
MR ≤2+ (core lab)	80.9% (38/47)	82.9% (29/35)
∆ LVEDV (ml)	-2 ± 26 (36 paired)	-7 ± 33 (22 paired)
∆ 6MWD (m)	13 ± 112 (45 paired)	15 ± 94 (32 paired)
∆ KCCQ	14 ± 26 (49 paired)	13 ± 17 (37 paired)

Potential Pivotal Trial Pathways for Transcatheter MV Therapies

Primary MR (DMR)

Single-arm study in pts at prohibitive surgical risk (STS ≥8 or conditions precluding surgery) and high surgical risk (STS 4-<8); endpoint = objective performance criteria, OR
Non-inferiority RCT vs. surgical MV repair

Functional MR

Superiority RCT vs. GDMT, OR
Non-inferiority trial vs. MitraClip (if COAPT positive)

Endpoints for both

Composite clinical + surrogate outcomes,
in pts with sustained MR reduction

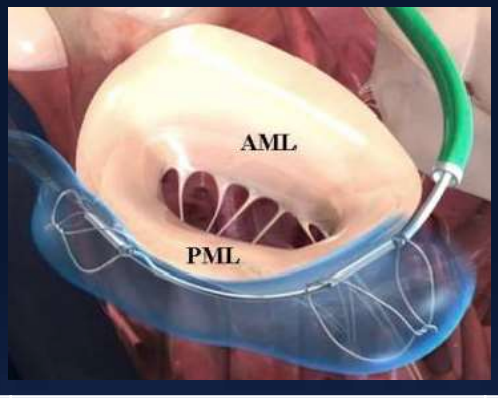
Considerations for Effectiveness Endpoints

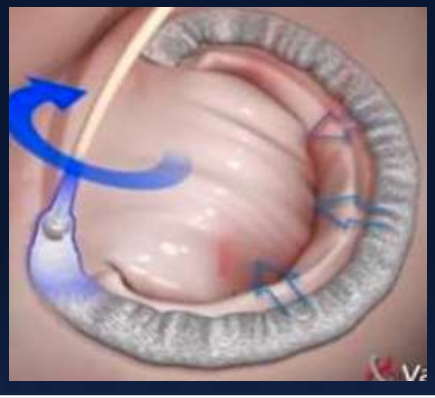
Hierarchical analysis based on
importance and strength of surrogacy

1. Freedom from death >
2. Freedom from HF hospitalization >
3. ⇑ 6MWD >
4. Improved QoL measures (eg KCCQ) >
5. ⇓ LVEDV >
6. ⇓ BNP or NT-pro BNP

In patients with sustained MR reduction

Novel MV Repair Devices with Ongoing/Soon to Begin US Pivotal Randomized Trials





	Cardiac Dimensions Carillon	Edwards/Valtech Cardioband	NeoChord DS1000
Mechanism and Indication	Coronary sinus mediated posterior annulus cinching for FMR	LA semi-rigid posterior partial annuloplasty band with anchor cinching for FMR	Transapical PTFE neochords for DMR
IDE	Approved	Approved	Approved

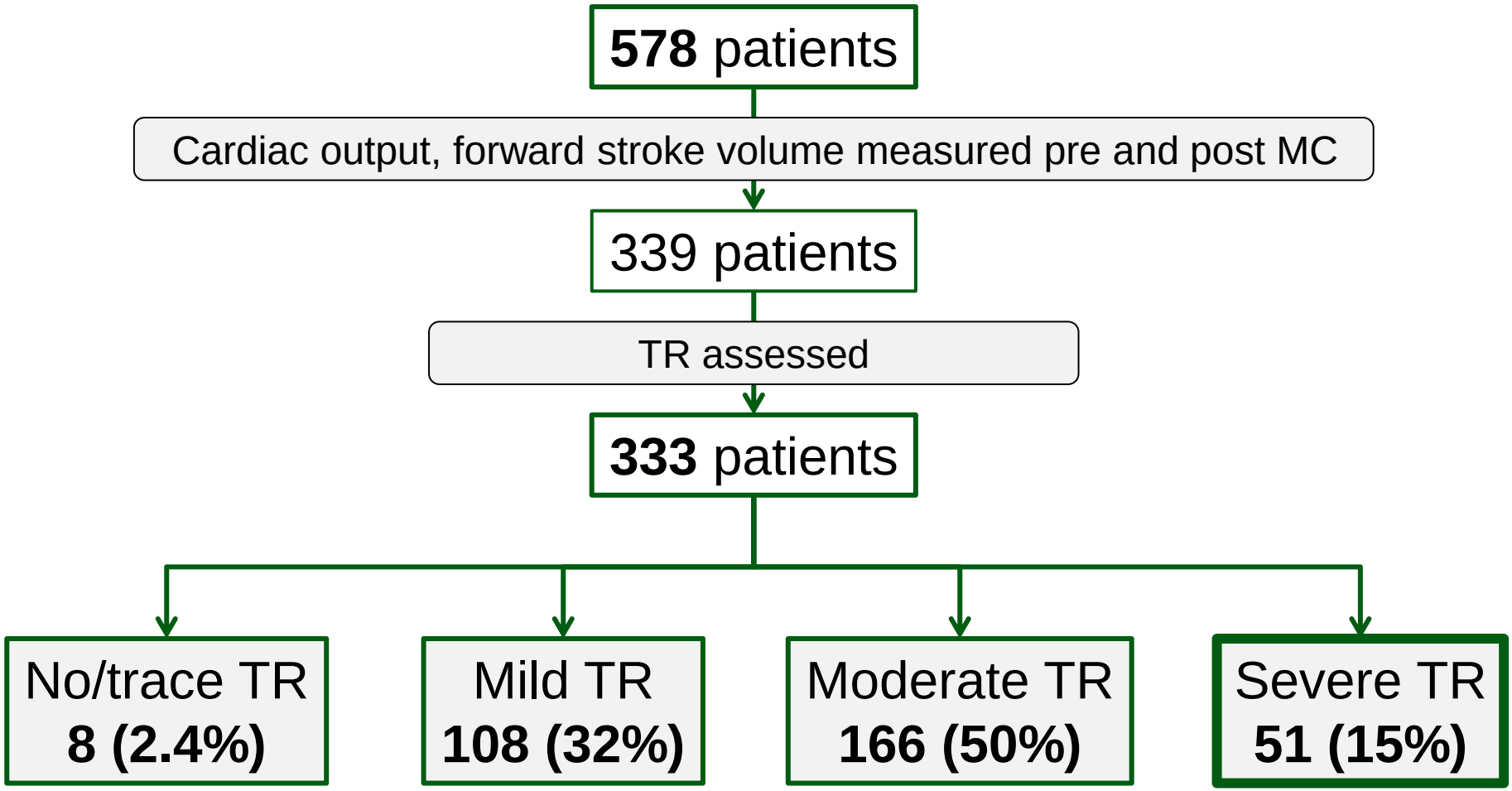
TRICUSPID REGURITATION

Etiology

- Primary - DTR (25%)
  - Ebstein's anomaly
  - Carcinoid tumors
  - Infective endocarditis
  - Drug related "Fen-phen" diet pills
  - Radiation therapy
  - Rheumatic
  - Iatrogenic
    - Pacemaker, ICD, Biopsy
- Secondary - FTR (75%)
  - Left heart disease
  - Right heart dysfxn
  - Pulmonary hypertension
    - Chronic jung disease
    - Thromboembolism
  - Annular dilation
    - Usually from A-fib

Tricuspid Regurgitation in Patients Undergoing MitraClip Therapy for MR at AK St. Georg

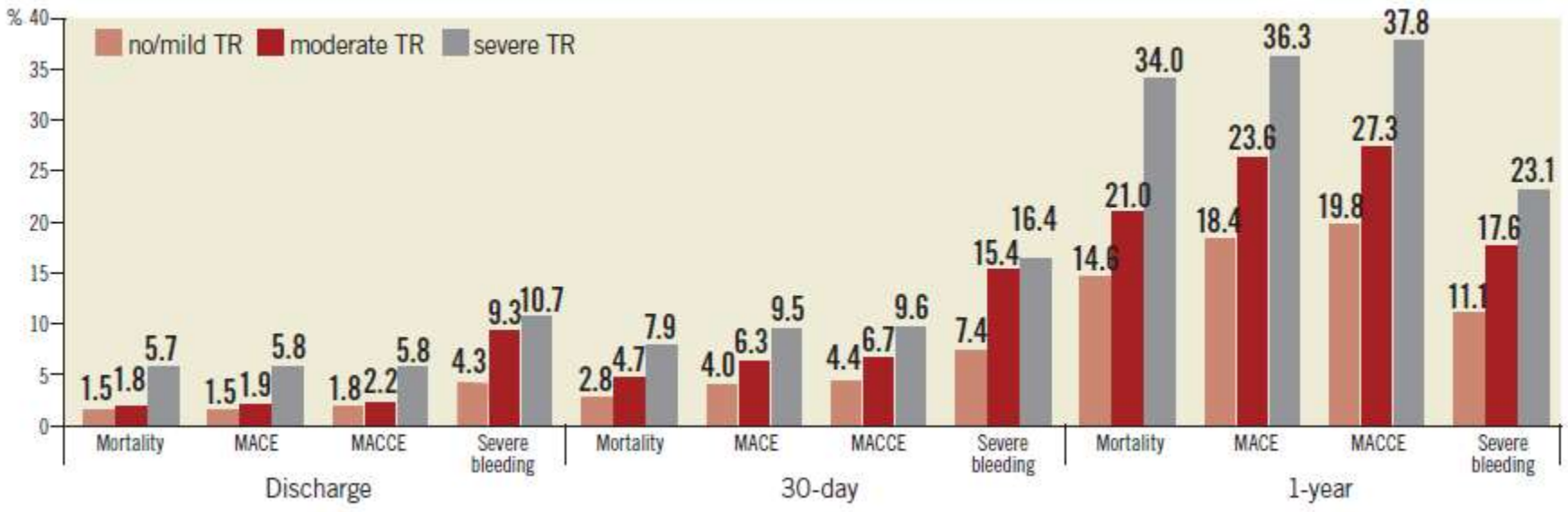
- 09/2009 – 11/2015



Impact of Tricuspid Regurgitation on Outcomes after MitraClip Therapy for MR in German TRAMI Registry

- 766 patients (08/2010 – 07/2013)

No/Mild TR	Moderate TR	Severe TR	
334 (44%)	**326 (43%)**	**106 (14%)**	
PHT: 42%	52%	59%	(*P*=0.01)
MC success: 85%	86%	77%	(*P*=0.11)



Kalbacher D et al. *Eurointervention* 2017

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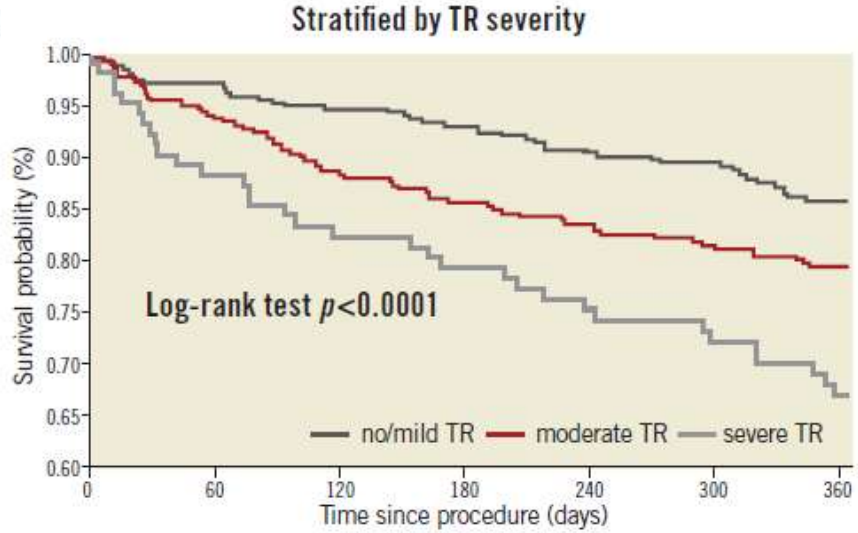


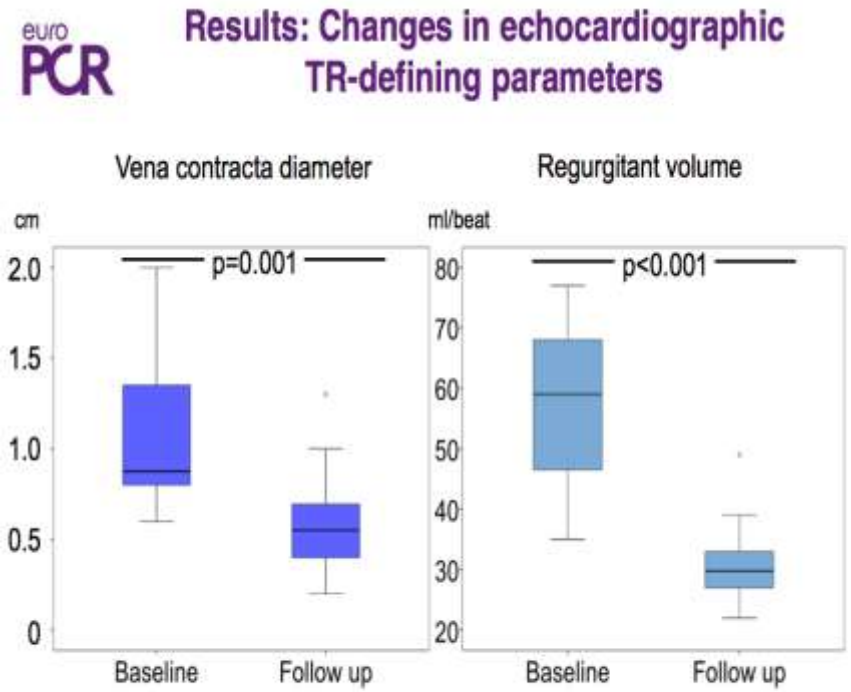
Kalbacher D et al. *Eurointervention* 2017

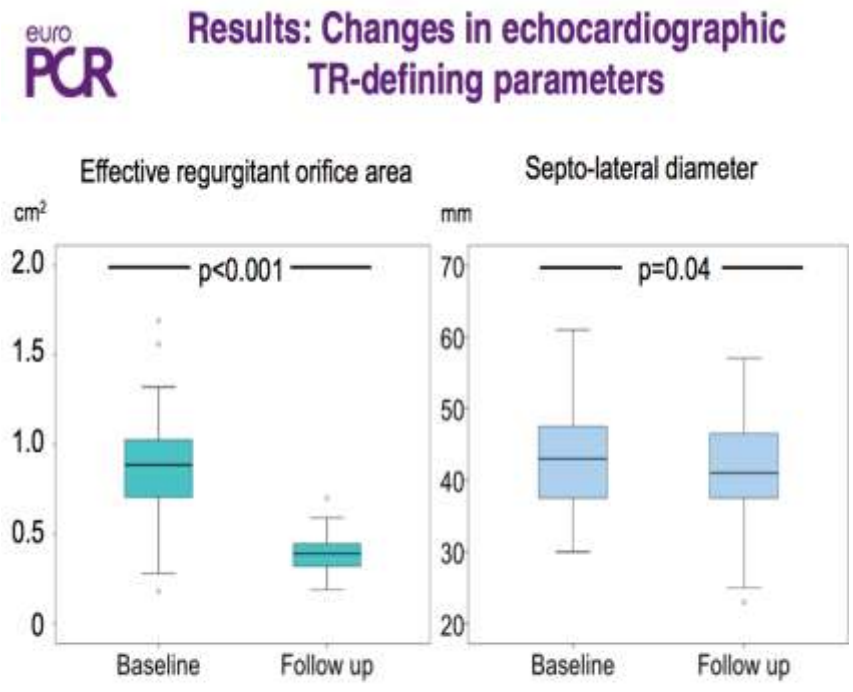
MITRACLIP in tricuspid position

- About 400 cases performed worldwide
- Transfemoral has become default approach
- Usually 1-2 clips on antero-septal leaflets (easiest to reach)
- Medial clip has better results than commissural clip but not always feasible
- TEE is standard and superior to ICE:
  - transgastric view is important in understanding location of TR, planning procedure, and deciding which leaflets to clip
- Patient selection is important
- Challenges:
  - Leaflets are more fragile, larger coaptation gap
  - Imaging not standardized
- New device with longer arms and a tricuspid delivery system are needed

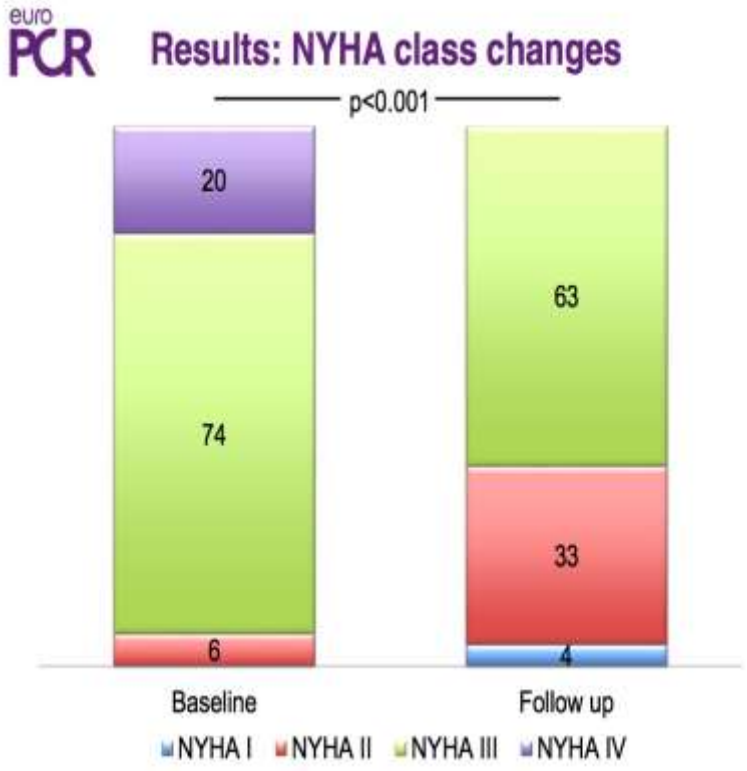
Nickenig et al. Circulation 2017

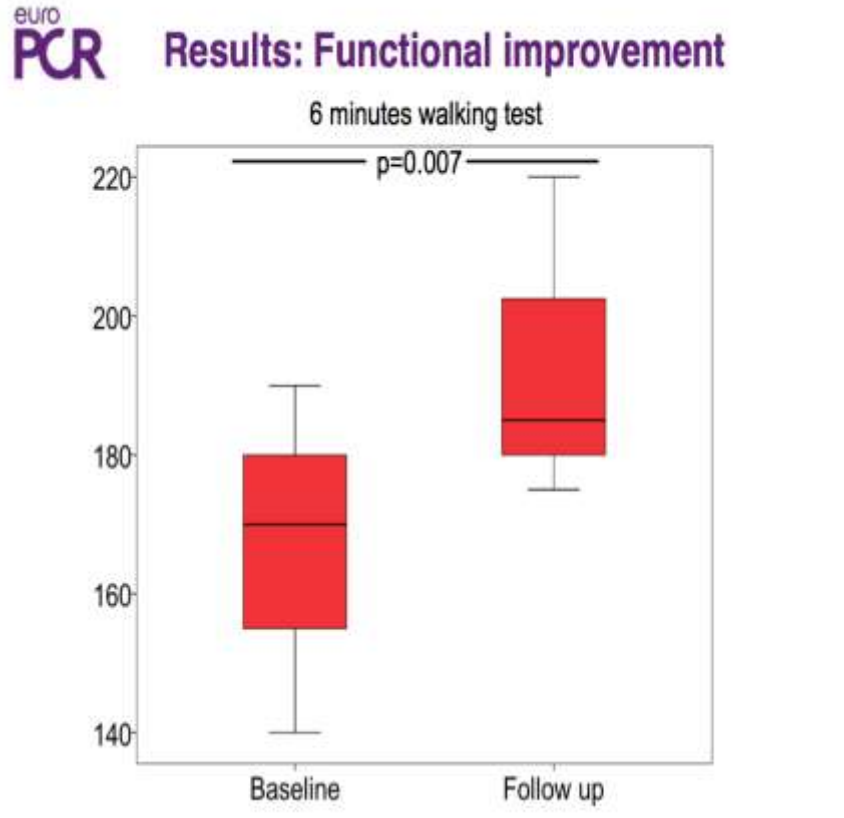
TR Reduction



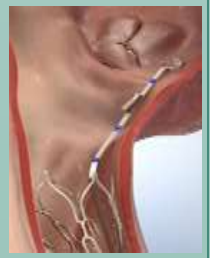


Clinical improvement



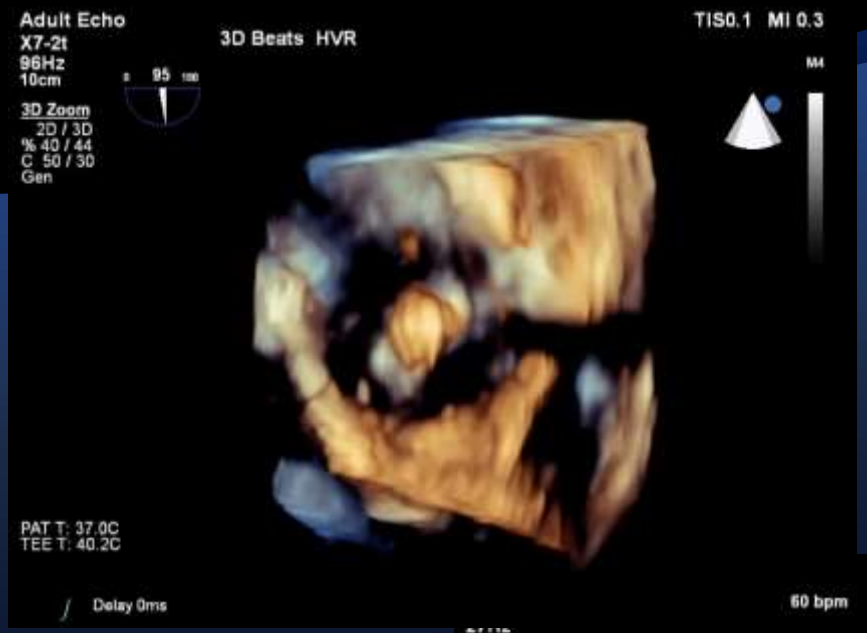


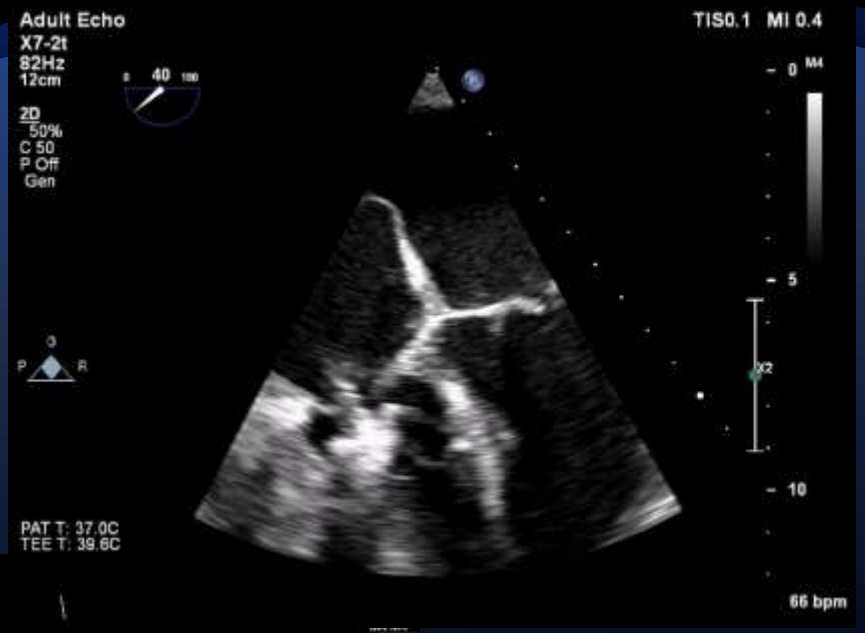
Tricuspid repair devices

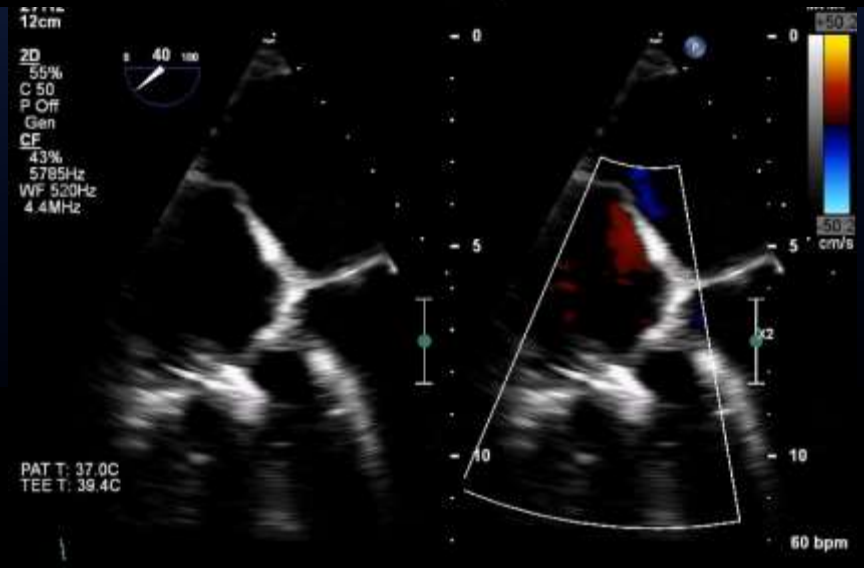
Device Name	MitraClip	Trialign	TriCinch	Cardioband	Millipede	FORMA Repair System	Caval valve implantation	TRAIPTA
Device Image								
Description	Bicuspidisation of the TV by plicating	Bicuspidisation of the TV by plicating	Bicuspidisation of the TV by cinching	Direct annuloplasty device	Complete semi rigid ring	Spacer to occupy the regurgitant orifice area	Caval valve implantion in vena cava	Pericardial circumferential device
Access	Transfemoral	Transjugular	Transfemoral	Transfemoral	Transfemoral	Transsubclavian	Transjugular/ transfemoral	Transjugular/ transfemoral
Status*	• About 60 patients	• About 15 patients	• About 25 patients	• About 10 patients	• About 2 patients	• About 20 patients	• About 40 patients	• Only pre-clinical data

*** At the moment of reporting from recently international meeting**

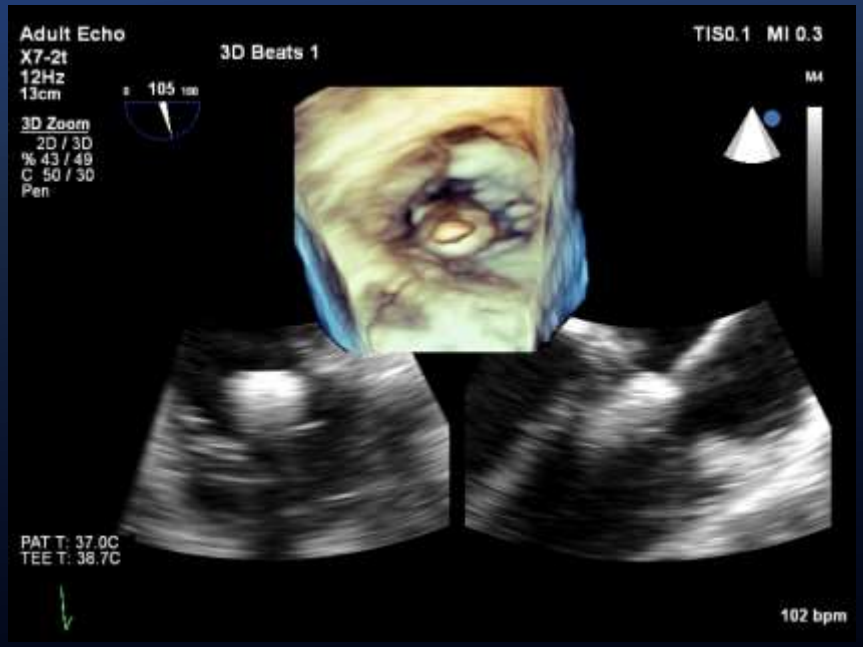
Clip 1

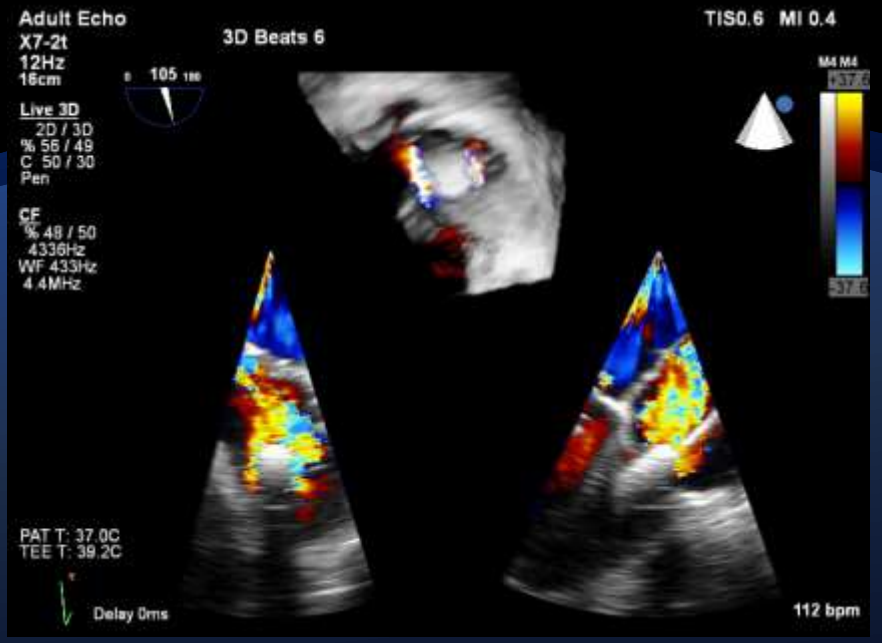

Adult Echo
X7-2t
96Hz
10cm
3D Zoom
2D / 3D
% 40 / 44
C 50 / 30
Gen
3D Beats HVR
TIS0.1 MI 0.3
PAT T: 37.0C
TEE T: 40.2C
Delay 0ms
60 bpm

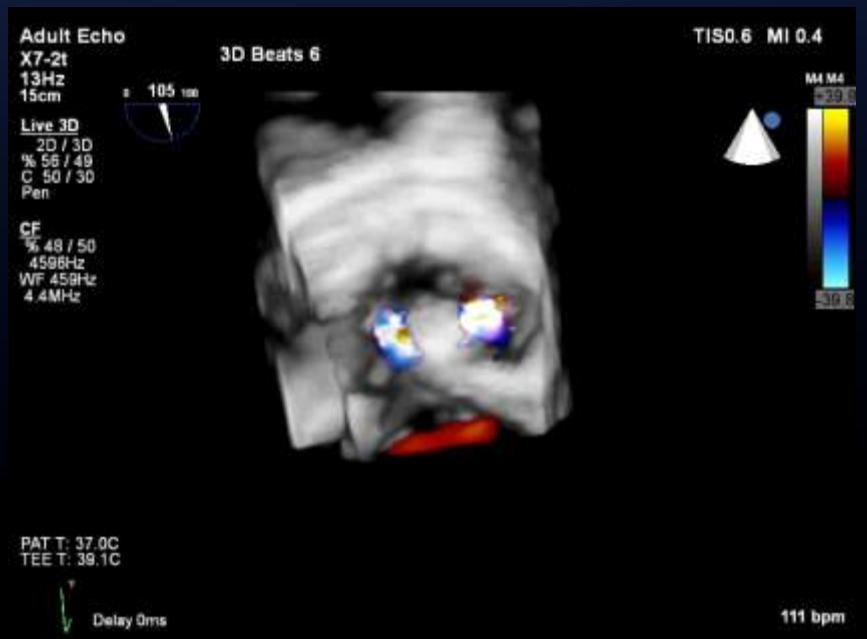

Adult Echo
X7-2t
82Hz
12cm
2D
50%
C 50
P Off
Gen
TIS0.1 MI 0.4
PAT T: 37.0C
TEE T: 39.6C
66 bpm


12cm
2D
55%
C 50
P Off
Gen
CF
43%
5785Hz
WF 520Hz
4.4MHz
cm/s
PAT T: 37.0C
TEE T: 39.4C
60 bpm

FORMA: Final Position



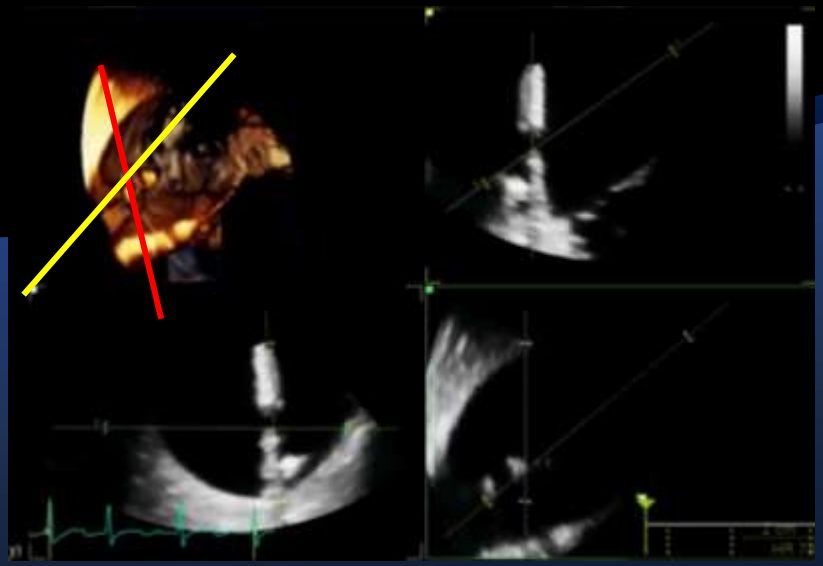




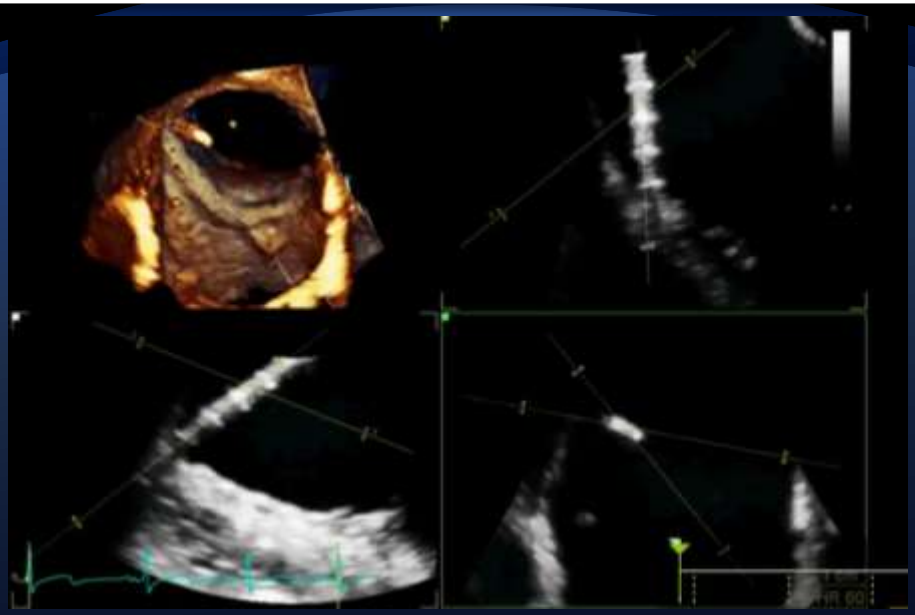
Total Residual EROA = 0.74 cm2

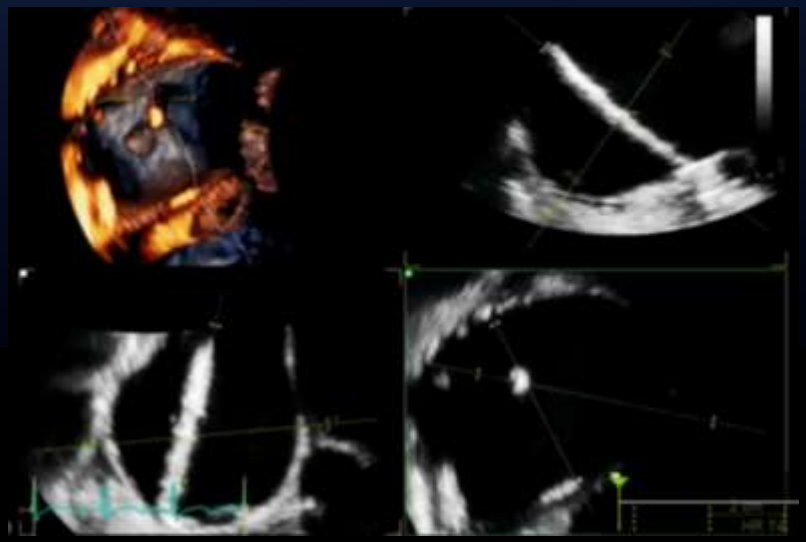
Cardioband TR

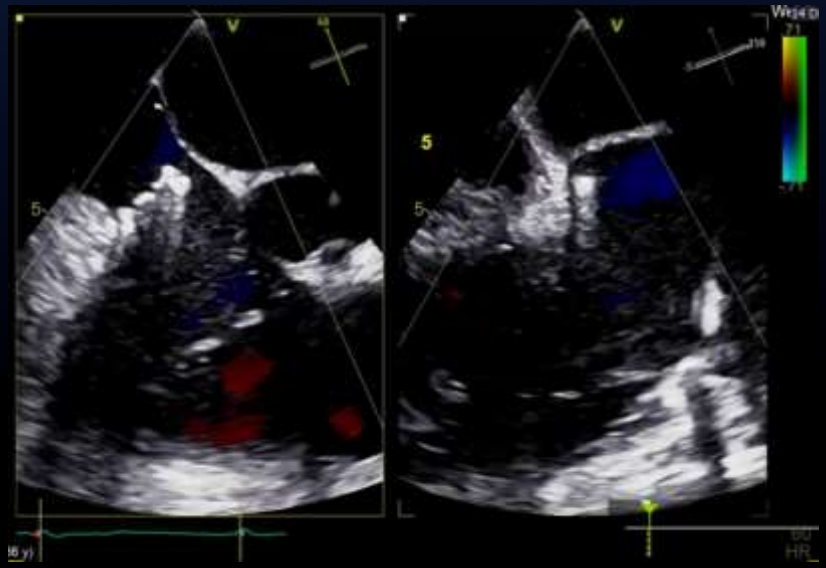
Tri-Repair CE EU trial enrolling in Germany, France and Italy



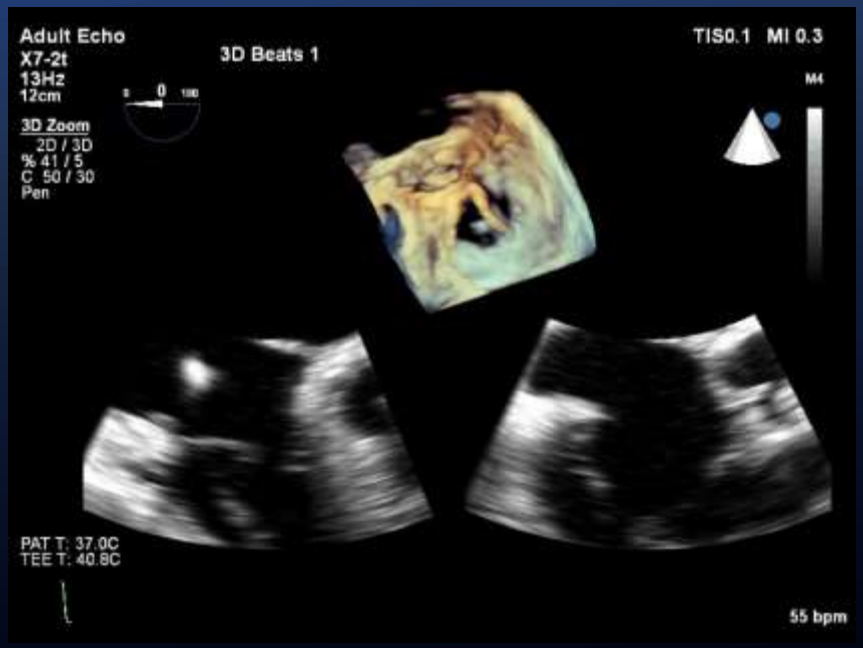
Tricuspid Valve View

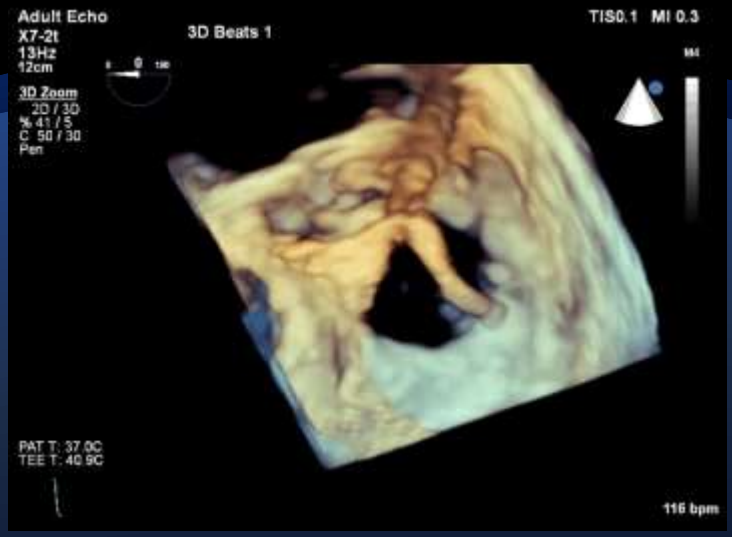


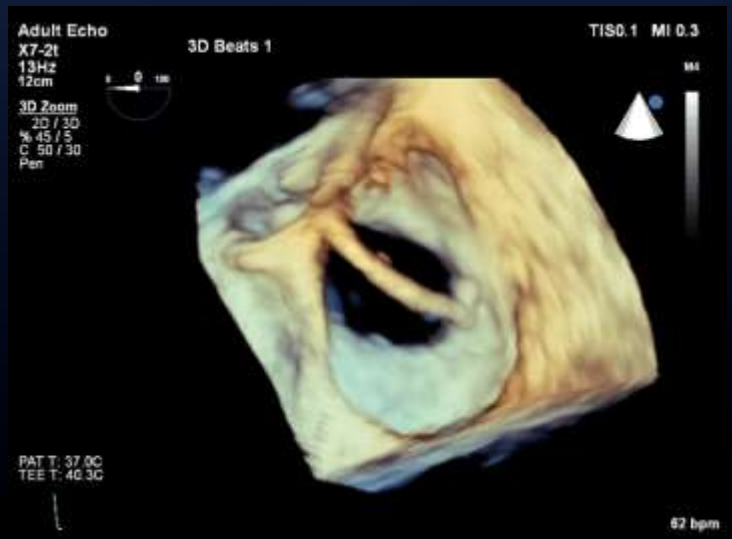




Trialign







Cinching--Plicating

trialign

Potential Pivotal Trial Pathways for Transcatheter TV Therapies

TR in association with DMR

Single-arm study in pts at prohibitive/high surgical risk for MV Repair (STS ≥6-8 or conditions precluding surgery); endpoint = objective performance criteria

Functional TR

Single-arm study in pts at prohibitive/high surgical risk for TV Repair (STS ≥6-8 or conditions precluding surgery); endpoint = objective performance criteria

PyeongChang 2018