Update on Transcatheter Treatment of Mitral and Tricuspid Regurgitation

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Disclosures

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Objectives

- Review the application of the commercially available technologies for the treatment of mitral and tricuspid valve disorders
- Review the investigational transcatheter valve repair and replacement technologies

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- Review the investigational transcatheter valve repair and replacement technologies

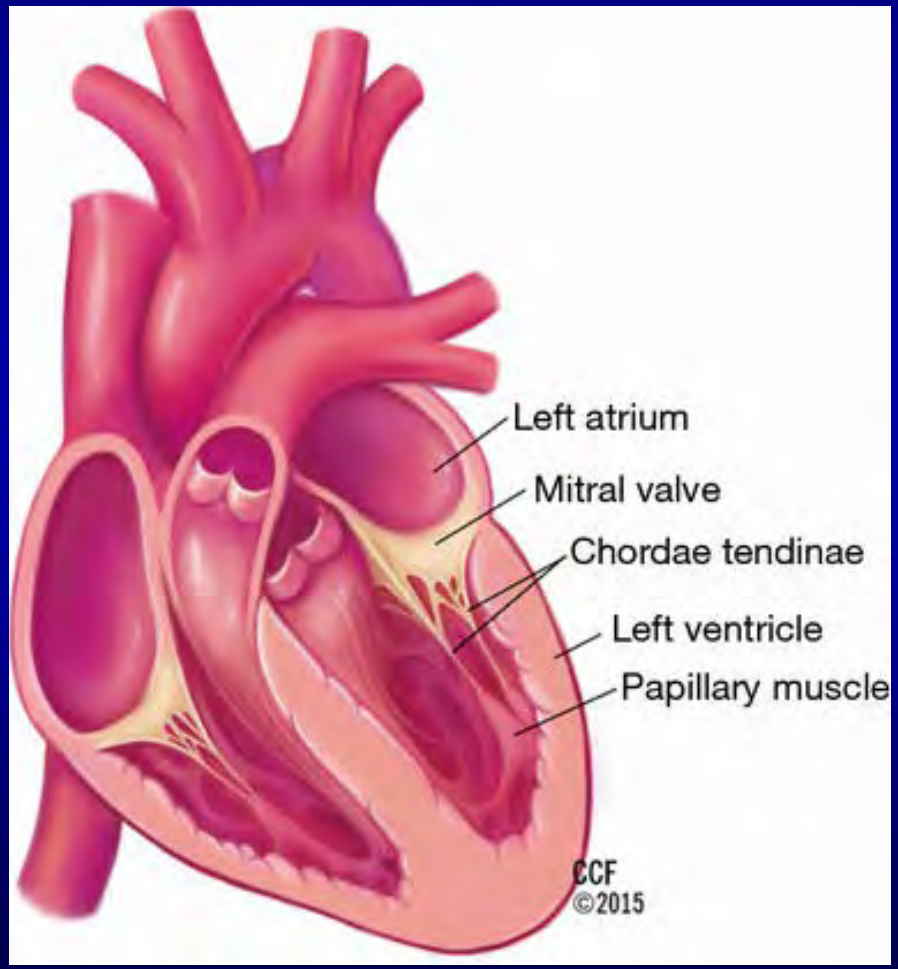
Transcatheter mitral valve repair and replacement

- Degenerative MR
- Functional MR
- Bioprosthetic mitral valve failure
- Degenerative mitral stenosis with MAC

Transcatheter tricuspid valve repair and replacement

- Functional TR
- Degenerative TR
- Bioprosthetic tricuspid valve failure

6 Anatomical Parts of the Mitral Valve



- Leaflets
- Annulus
- Chordae
- Papillary Muscles
- Left Ventricle
- Left Atrium

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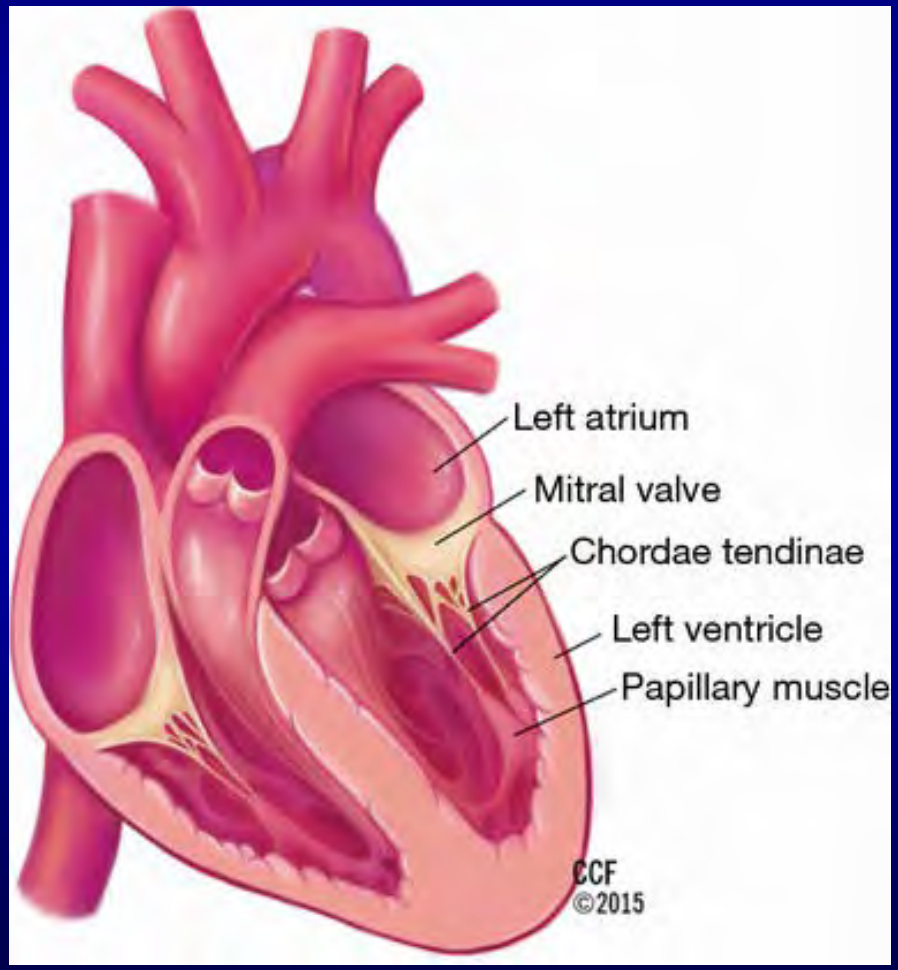

Transcatheter mitral valve repair

- Leaflet specific technologies
- Direct Annuloplasty
- Indirect/coronary sinus annuloplasty

- Leaflets
- Annulus
- Chordae
- Papillary Muscles
- Left Ventricle
- Left Atrium

Percutaneous Repair or Surgery for Mitral Regurgitation

Ted Feldman, M.D., Elyse Foster, M.D., Donald D. Glower, M.D., Saibal Kar, M.D., Michael J. Rinaldi, M.D., Peter S. Fail, M.D., Richard W. Smalling, M.D., Ph.D., Robert Siegel, M.D., Geoffrey A. Rose, M.D., Eric Engeron, M.D., Catalin Loghin, M.D., Alfredo Trento, M.D., Eric R. Skipper, M.D., Tommy Fudge, M.D., George V. Letsou, M.D., Joseph M. Massaro, Ph.D., and Laura Mauri, M.D., for the EVEREST II Investigators*

EVEREST II trial
A2/P2 pathology

279 patients with moderate-severe or severe MR randomized in 2:1 manner to MitraClip or surgery (repair/replacement)

Early experience, lack of 3D TEE, learning curve

Event		Surgery	P Value
Primary efficacy end point			
Freedom from death, from surgery for mitral-valve dysfunction, and from grade 3+ or 4+ mitral regurgitation†	100 (55)	65 (73)	0.007
Death	11 (6)	5 (6)	1.00
Surgery for mitral-valve dysfunction‡	37 (20)	2 (2)	<0.001
Grade 3+ or 4+ mitral regurgitation	38 (21)	18 (20)	1.00

Feldman T. et al. NEJM 2011

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EVEREST II trial
A2/P2 pathology

MitraClip was safer than surgery

Event	Percutaneous Repair	Surgery	P Value
	no. (%)		
Major adverse event at 30 days§			
Any major adverse event	27 (15)	45 (48)	<0.001¶
Any major adverse event excluding transfusion	9 (5)	9 (10)	0.23

Feldman T. et al. NEJM 2011

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EVEREST II trial
A2/P2 pathology

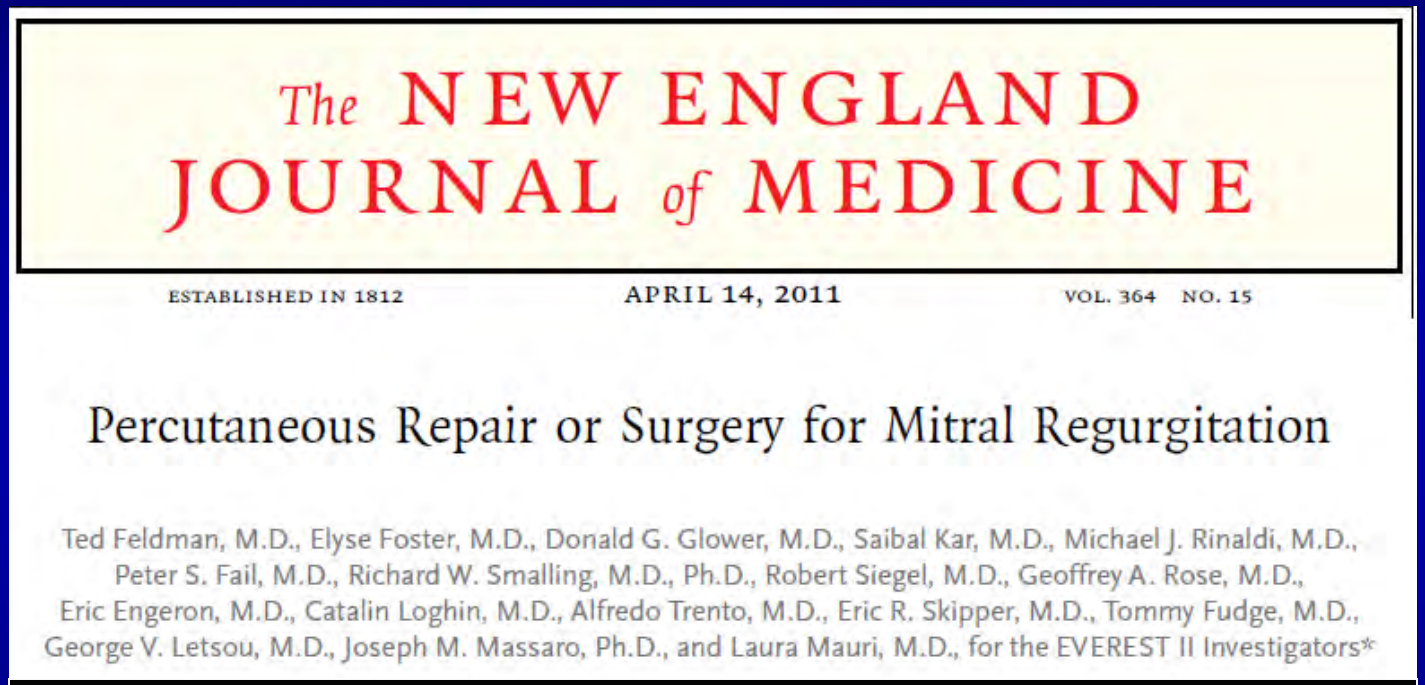
Comparable improvement in LV dimensions with both MitraClip and surgery

End Point	Percutaneous Repair (N=184)			Surgery (N=95)			P Value for Comparison between Study Groups
	No. of Patients	Value	P Value for Comparison between Baseline and 12 Mo	No. of Patients	Value	P Value for Comparison between Baseline and 12 Mo	
Change from baseline in left ventricular measurement							
End-diastolic volume — ml	144	−25.3±28.3	<0.001	66	−40.2±35.9	<0.001	0.004
End-diastolic diameter — cm	148	−0.4±0.5	<0.001	67	−0.6±0.6	<0.001	0.04
End-systolic volume — ml	144	−5.5±14.5	<0.001	66	−5.6±21.0	0.04	0.97
End-systolic diameter — cm	146	−0.1±0.6	0.06	67	−0.0±0.6	0.86	0.38
Ejection fraction — %	144	−2.8±7.2	<0.001	66	−6.8±10.1	<0.001	0.005

Feldman T. et al. NEJM 2011

EVEREST II one year results

279 patients randomized to MitraClip (n=184) or surgery (n=95)



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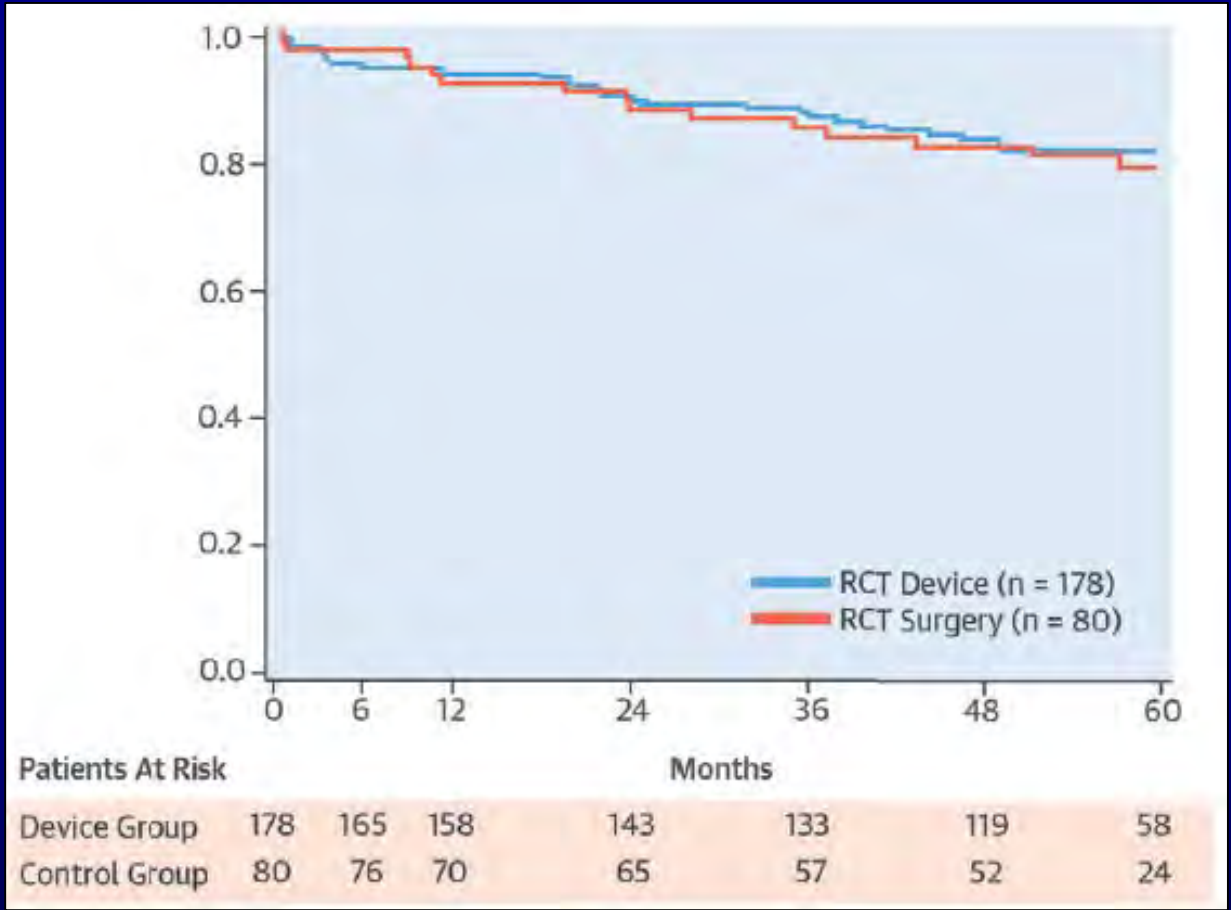
MitraClip versus Surgery for MR

- Safer
- Less reduction of MR
- Equivalent Clinical benefits

Randomized Comparison of Percutaneous Repair and Surgery for Mitral Regurgitation

5-Year Results of EVEREST II



Patients At Risk							
Device Group	178	165	158	143	133	119	58
Control Group	80	76	70	65	57	52	24

Freedom from mortality

No difference at 5 years

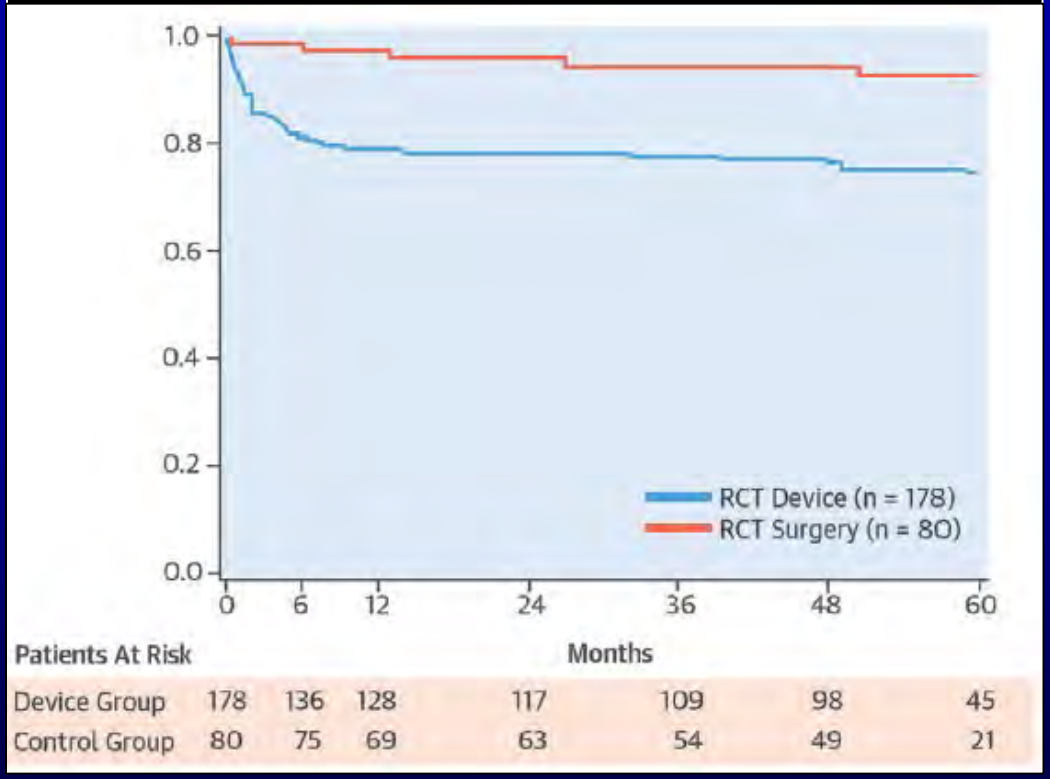
Feldman T. et al. JACC 2015

Randomized Comparison of Percutaneous Repair and Surgery for Mitral Regurgitation

5-Year Results of EVEREST II

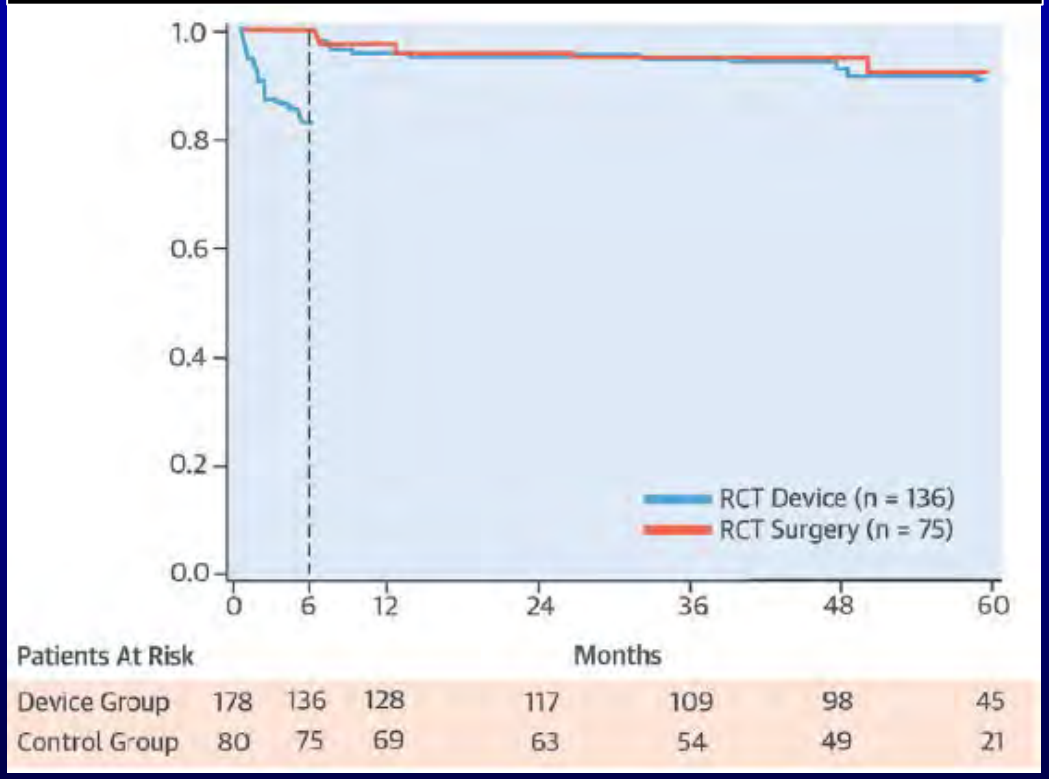
Freedom from surgery

Surgery superior to MitraClip



Landmark analysis for freedom from surgery beyond 6 months

No difference from 6mnths to 5 years



Feldman T. et al. JACC 2015

FDA IFU for MitraClip
US approval in October 2013

II. INDICATIONS FOR USE

The MitraClip Clip Delivery System is indicated for the percutaneous reduction of significant symptomatic mitral regurgitation (MR ≥ 3+) due to primary abnormality of the mitral apparatus [degenerative MR] in patients who have been determined to be at prohibitive risk for mitral valve surgery by a heart team, which includes a cardiac surgeon experienced in mitral valve surgery and a cardiologist experienced in mitral valve disease, and in whom existing comorbidities would not preclude the expected benefit from reduction of the mitral regurgitation.

Outcomes With Transcatheter Mitral Valve Repair in the United States

An STS/ACC TVT Registry Report

Paul Sorajja, MD,[a] Sreekanth Vemulapalli, MD,[b] Ted Feldman, MD,[c] Michael Mack, MD,[d] David R. Holmes, Jr, MD,[e] Amanda Stebbins, MS,[b] Saibal Kar, MD,[f] Vinod Thourani, MD,[g] Gorav Ailawadi, MD[h]

2952 patients treated at 145 hospitals btw 11/2013—09/2015

- **In-hospital mortality… 2.7%**
- **Procedure success…. 91.8%**
- **SLDA…….. 1.5%**
- **Length-of-stay..... 2 d (1,5 d)**
- **Home discharge..... 85.9%**

Sorajja P. et al. JACC 2017

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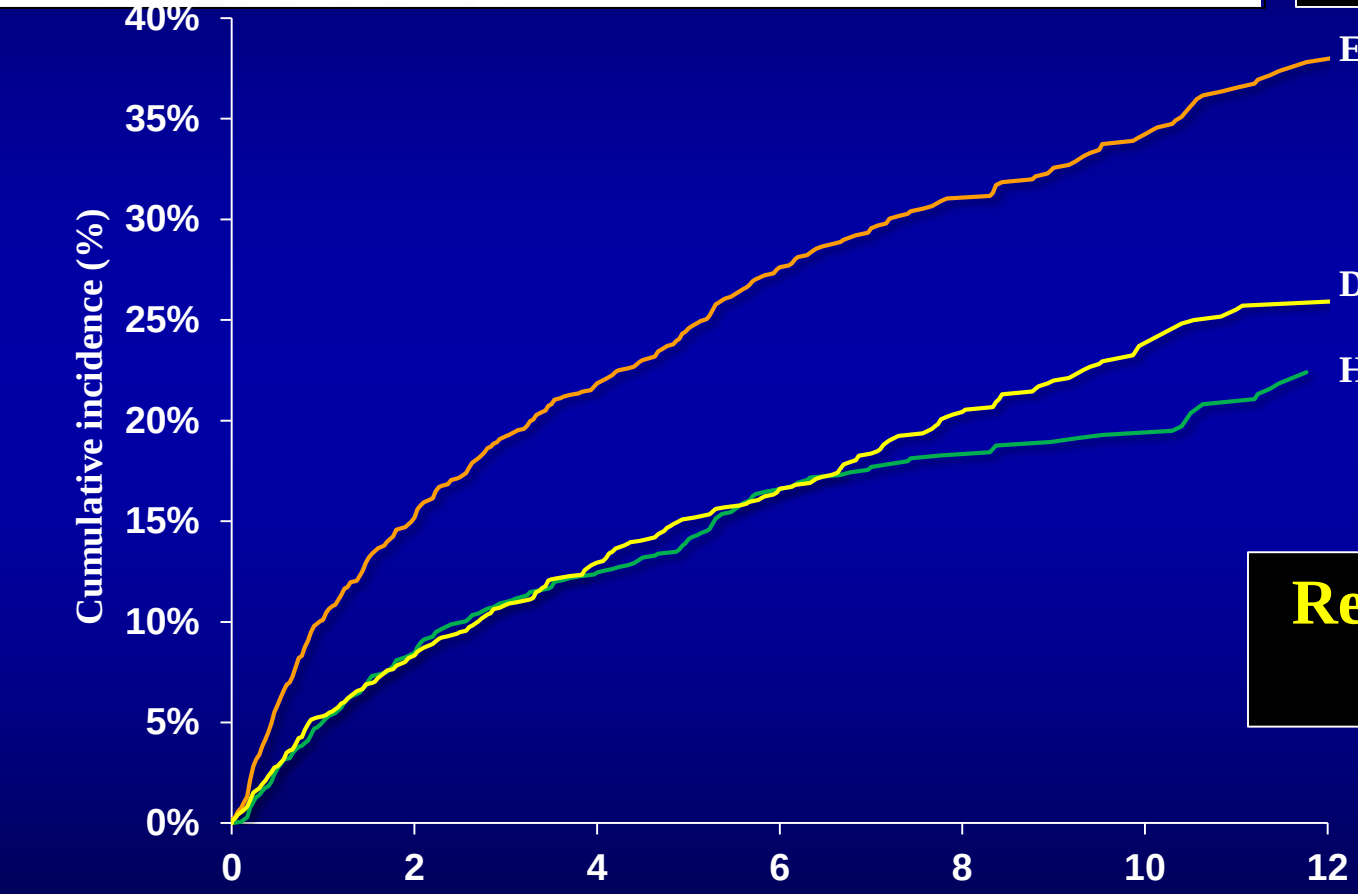

Repeat MitraClip = 6.2%
MV surgery = 2.1%

Sorajja P. et al. JACC 2017

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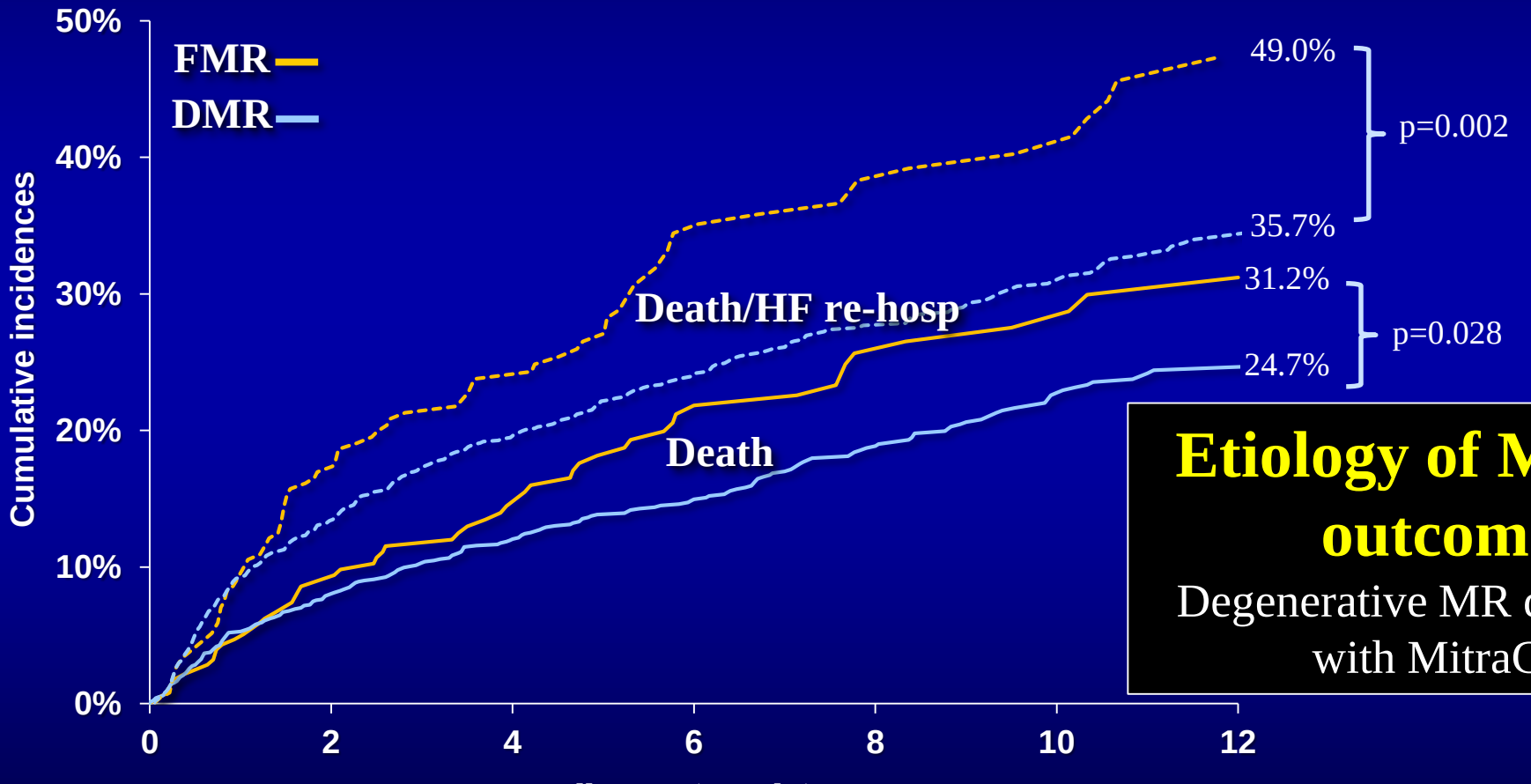

Etiology of MR and outcomes

Degenerative MR does better with MitraClip

No. at risk

FMR	297	196	123	73	40
DMR	1485	1024	726	472	287

Sorajja P. et al. JACC 2017

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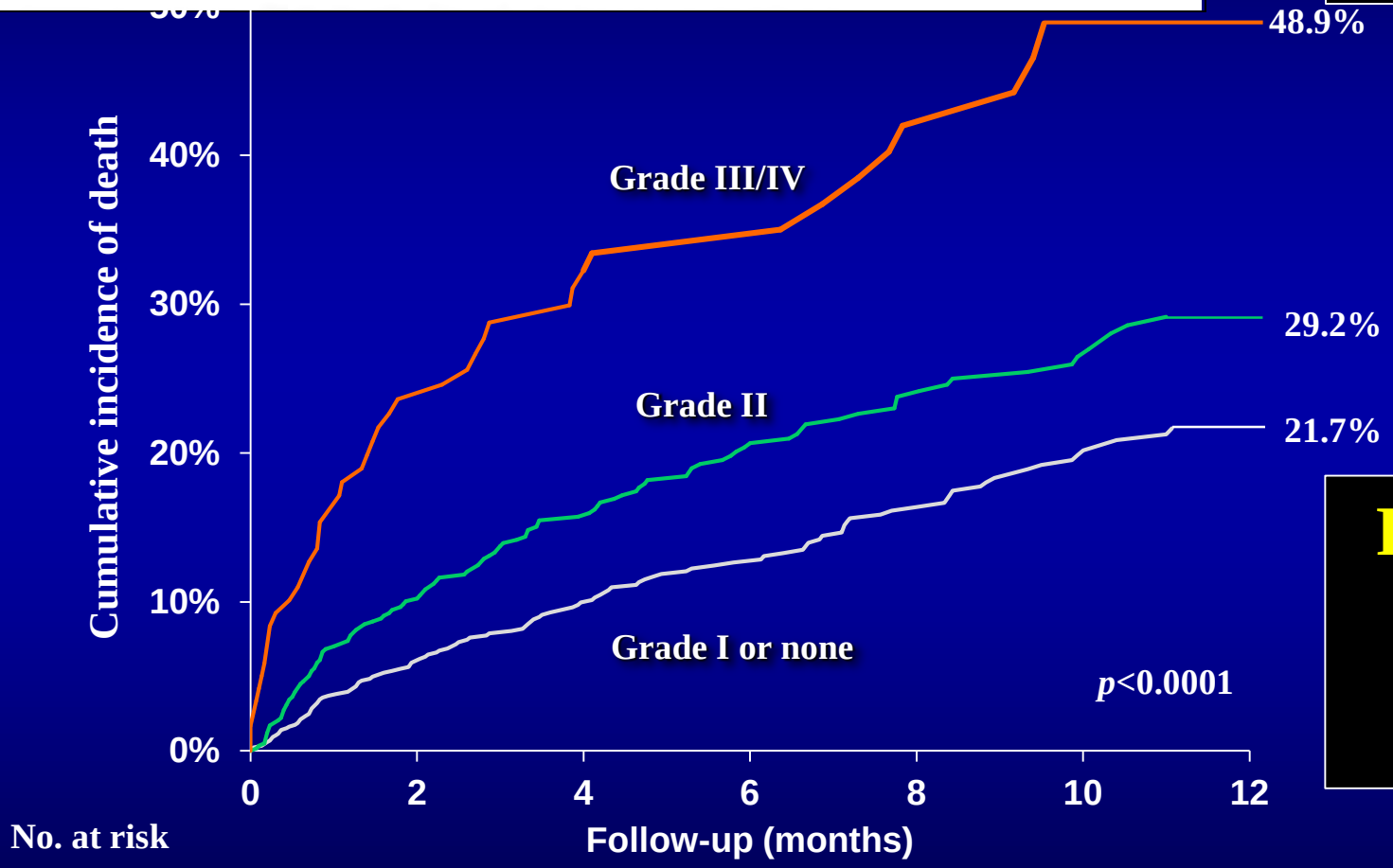


No. at risk					
III/IV	591	65	47	25	17
II	114	408	278	168	104
0/I	1146	810	559	373	213

Post-procedure MR and survival

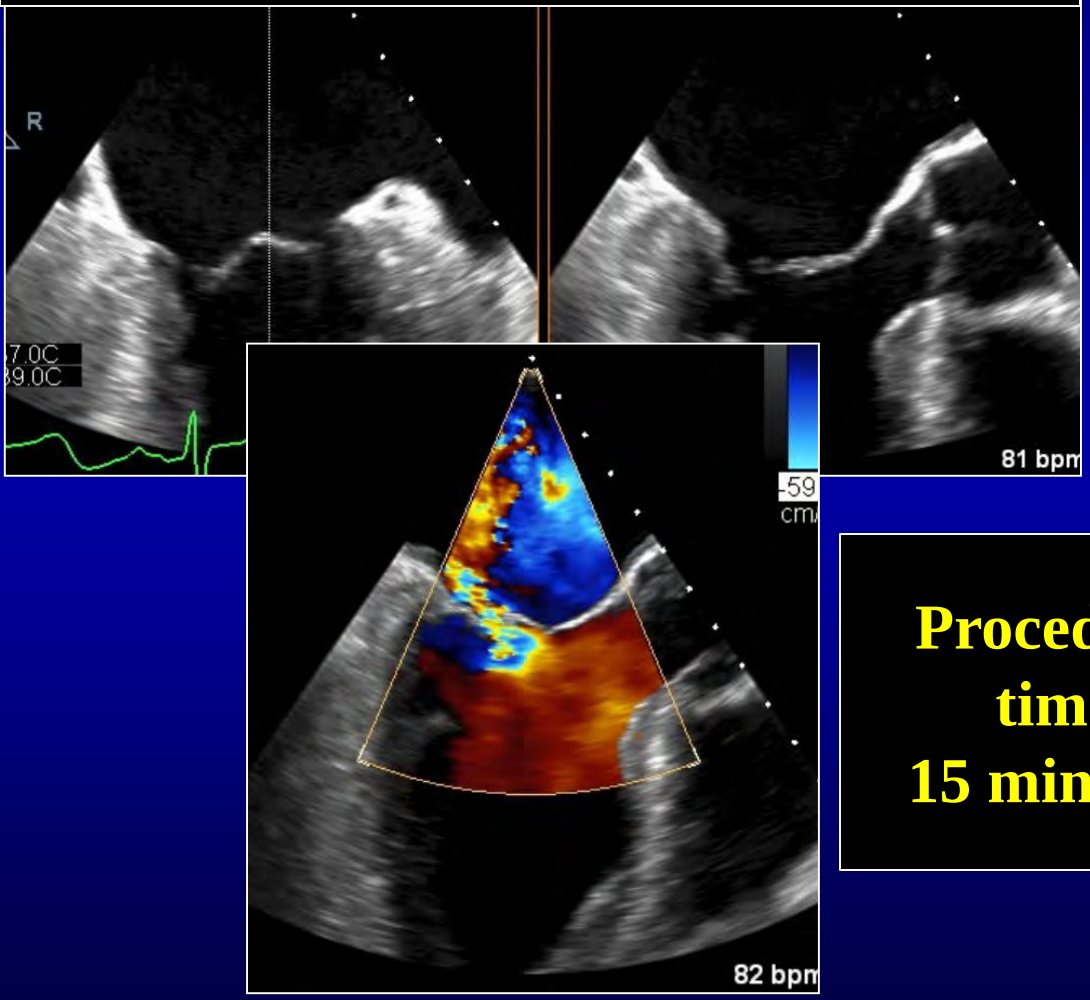
Worse survival with greater residual MR

Sorajja P. et al. JACC 2017

70 y/o male with flail of A2

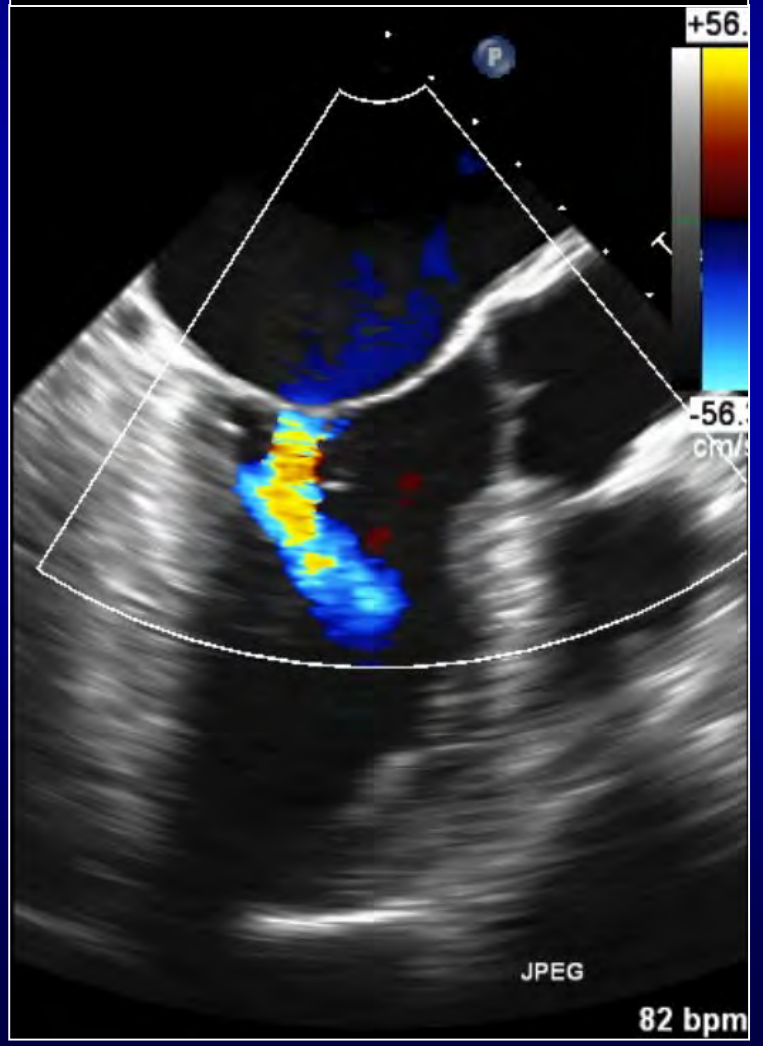
EVEREST like patient

Flail of A2 with severe MR



Procedure time 15 minutes

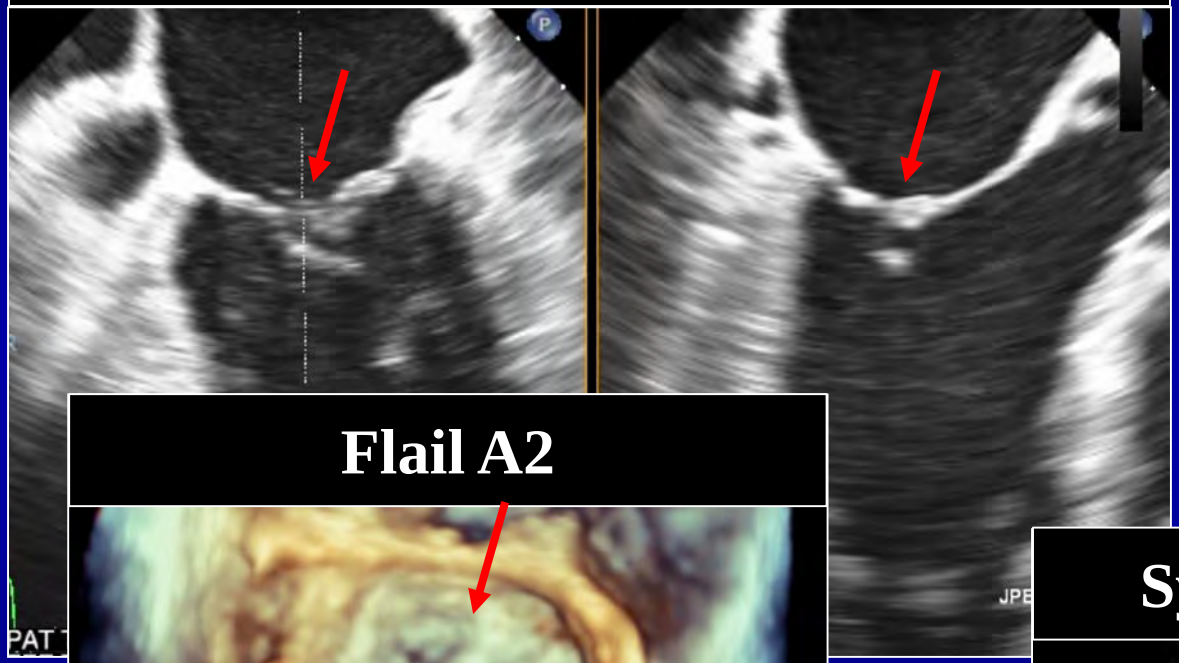
s/p 1 MitraClip
Trivial residual MR



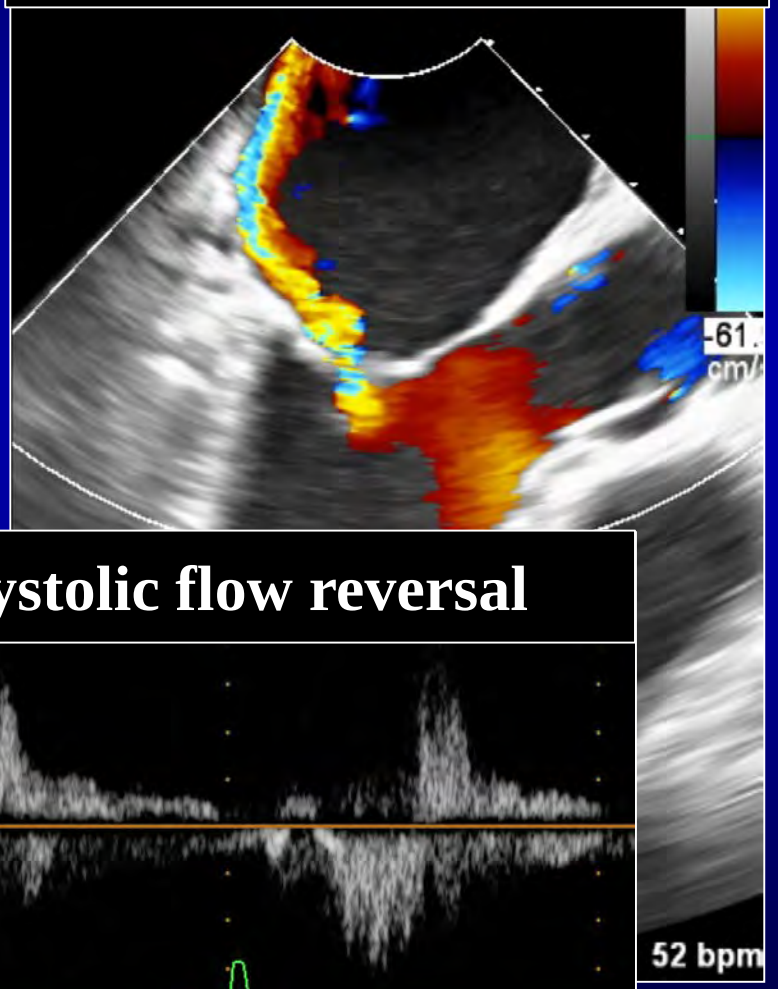
69 y/o male with heart failure, NYHA 3

Severe MR due to flail of A2

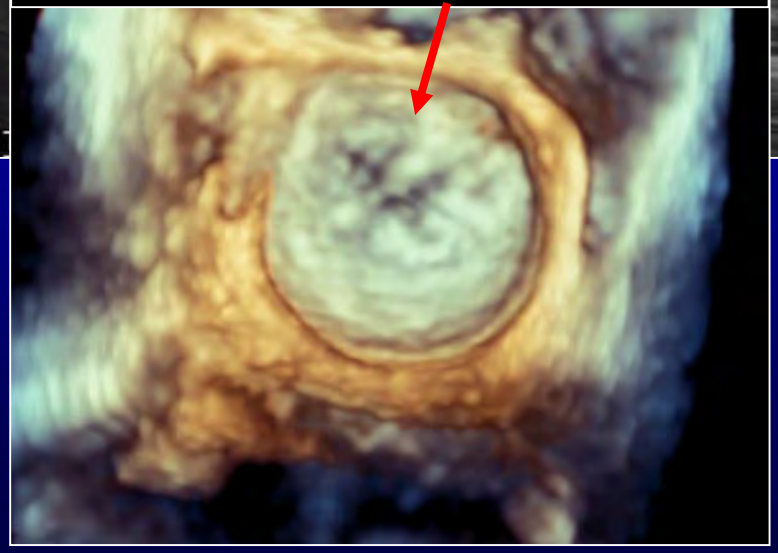
Flail A2



Severe MR



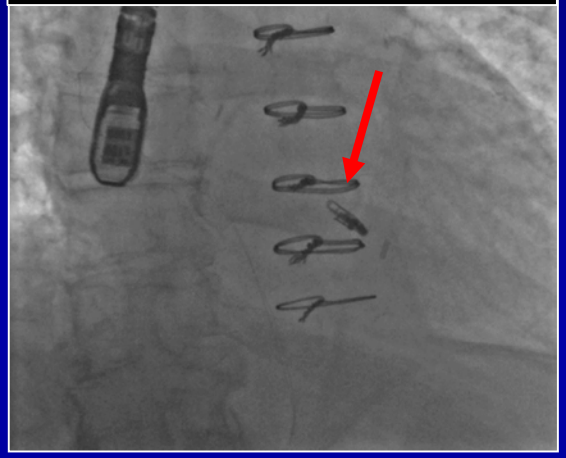
Flail A2

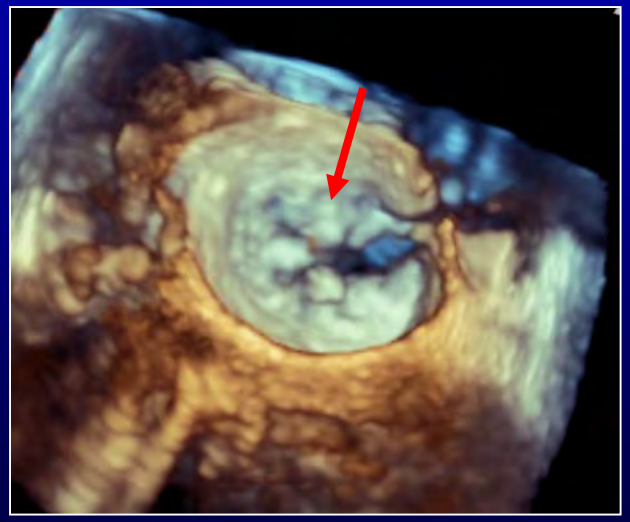


Systolic flow reversal

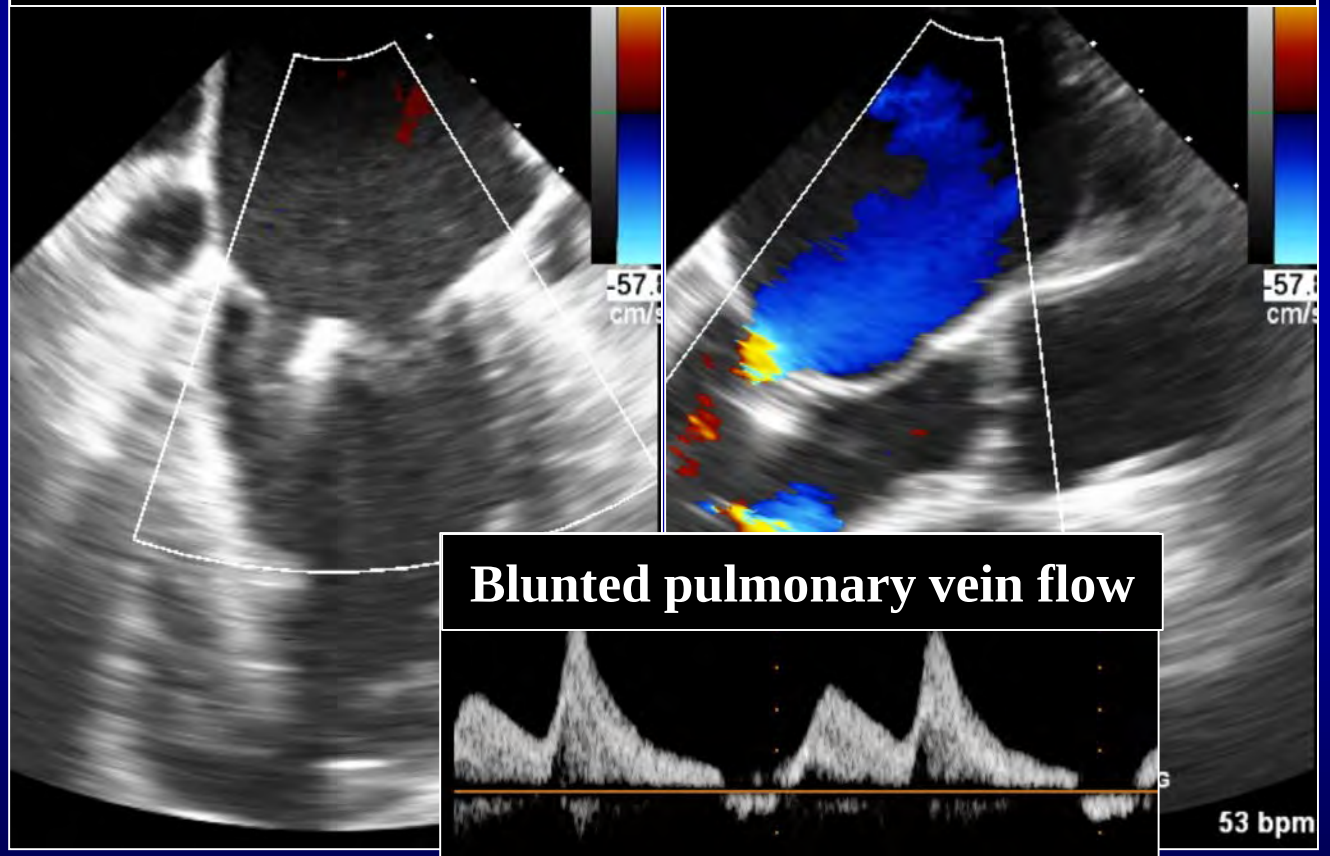
s/p transcatheter mitral valve repair with MitraClip x 1

s/p MitraClip x 1





Trivial residual MR



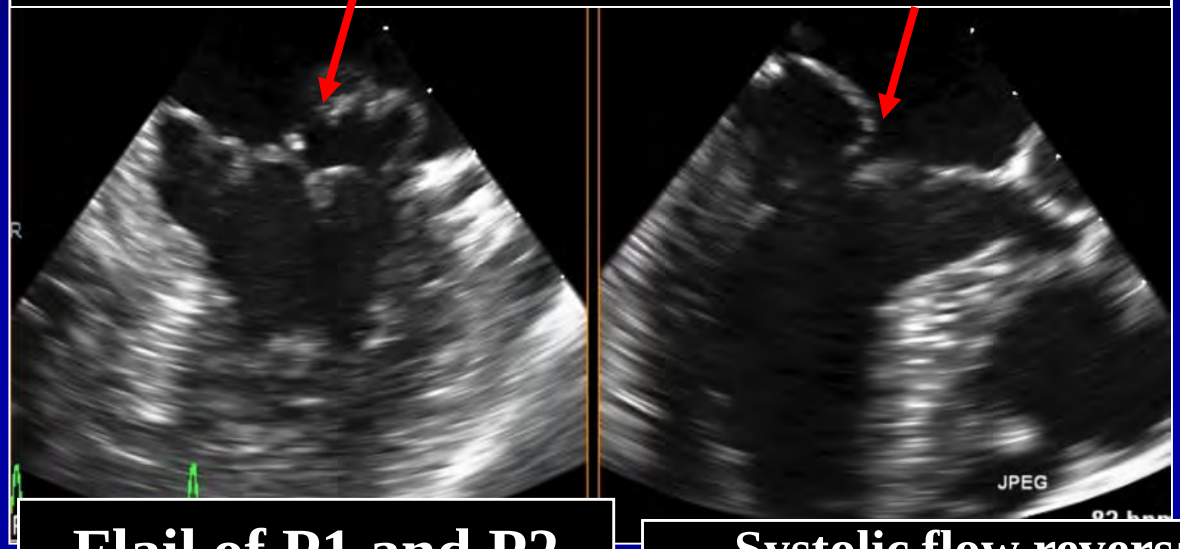
Blunted pulmonary vein flow

Expanded indications of the MitraClip: Beyond the A2/P2 EVEREST criteria

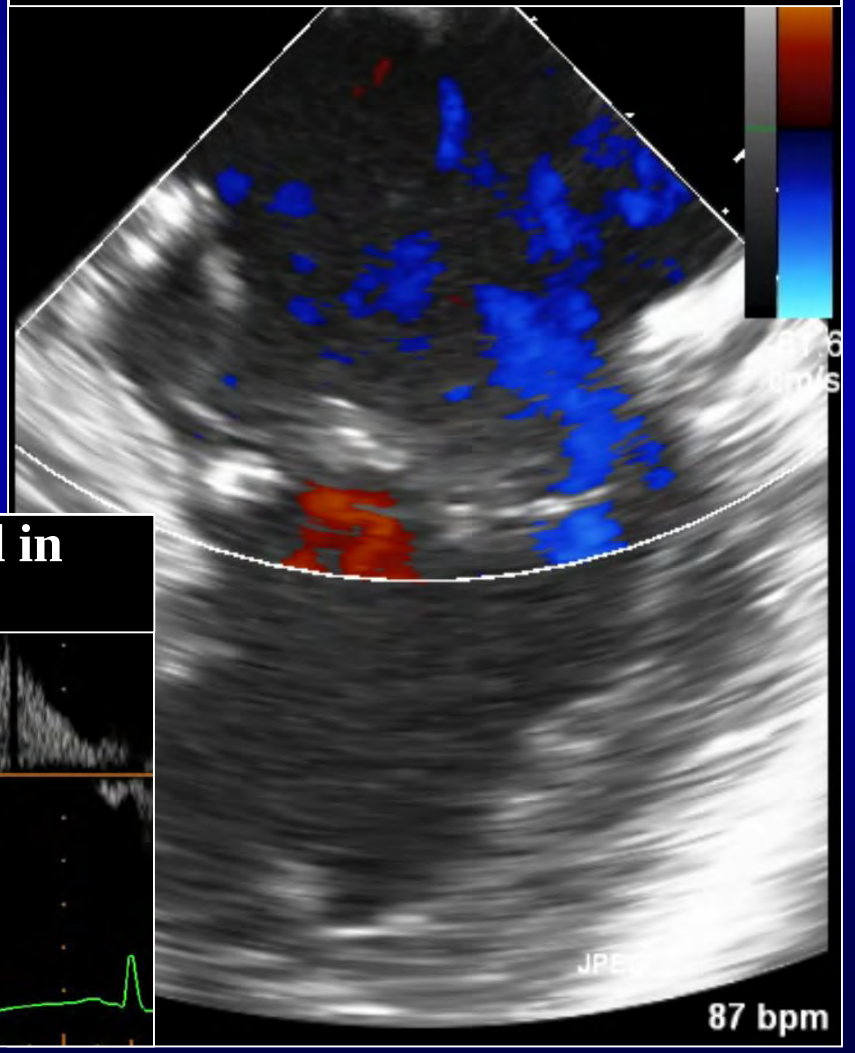
- A1P1 or A3P3 flail or prolapse
- Failed surgical repair
  - Ring annuloplasty or snapping of artificial chord
- Severe MR due to septal anterior motion in HOCM
- Post-MI Ruptured papillary muscle

81 y/o female with very severe MR

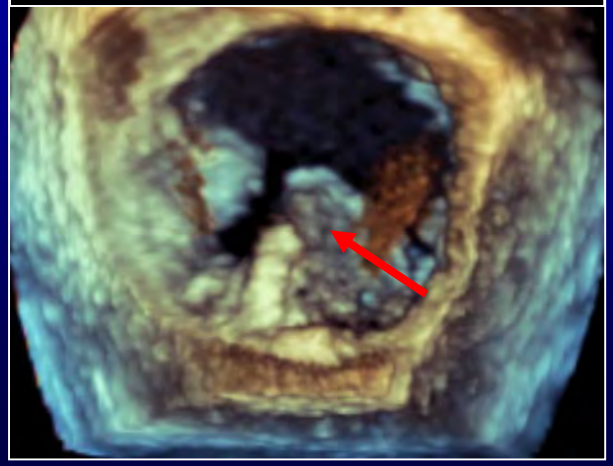
Flail of P1 and P2 with cordal rupture



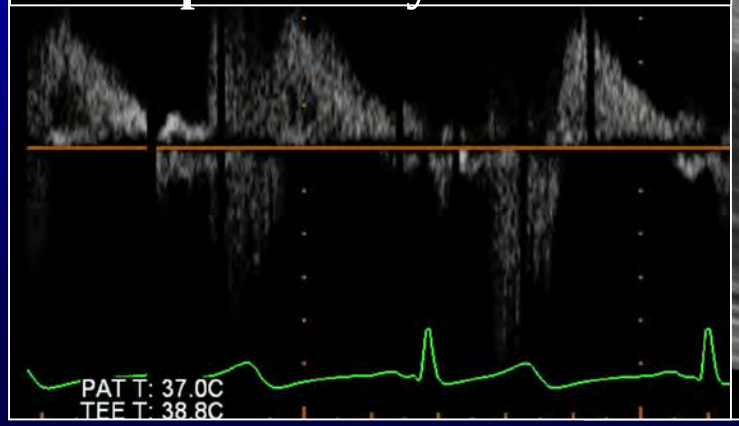
Very severe MR



Flail of P1 and P2

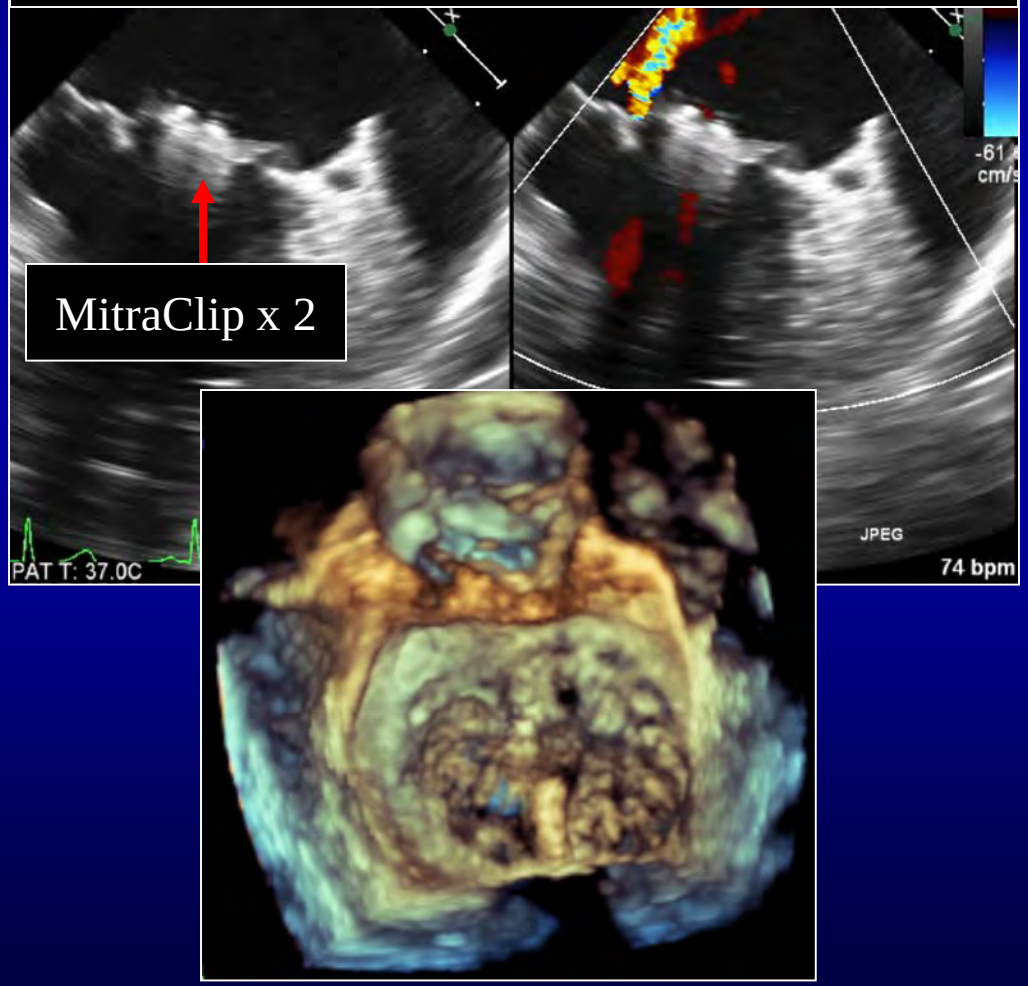


Systolic flow reversal in pulmonary veins

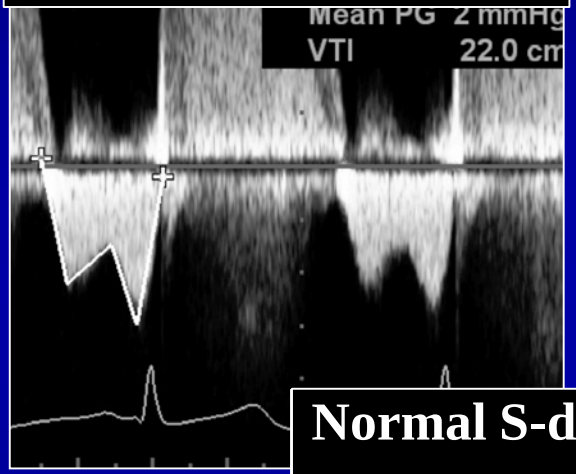


s/p MitraClip x 2

Mild residual MR



Mean mitral gradient 2mmHg



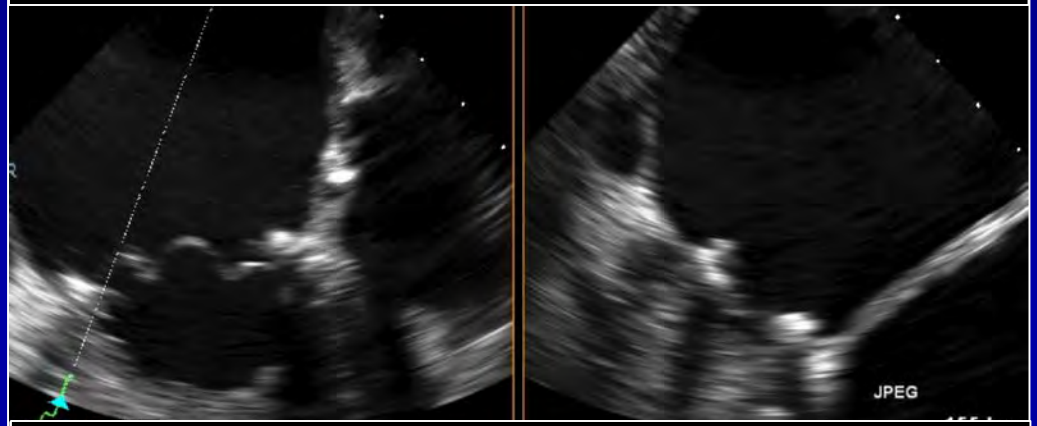
Normal S-dominant pulmonary vein flow

Expanded indications of the MitraClip: Beyond the A2/P2 EVEREST criteria

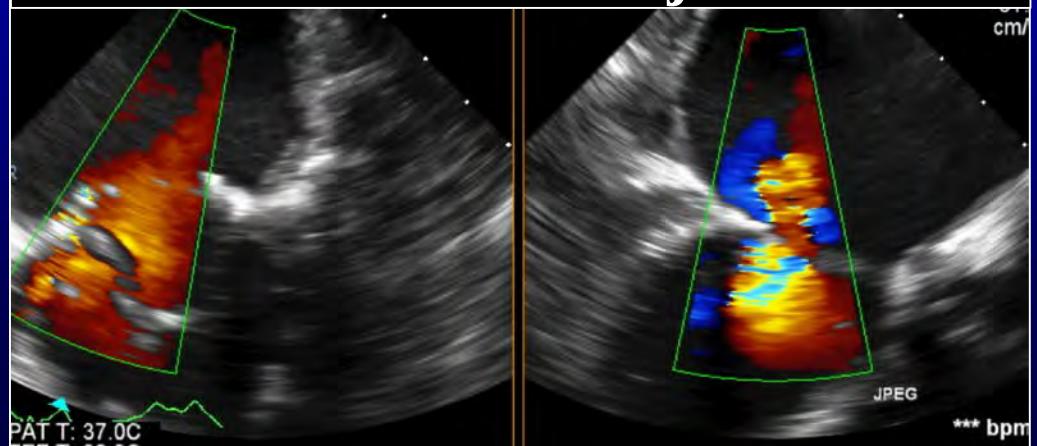
- A1P1 or A3P3 flail or prolapse
- Failed surgical repair
  - Ring annuloplasty or snapping of artificial chord
- Severe MR due to septal anterior motion in HOCM
- Post-MI Ruptured papillary muscle

79 y/o male with previous mitral valve ring presenting with shortness of breath

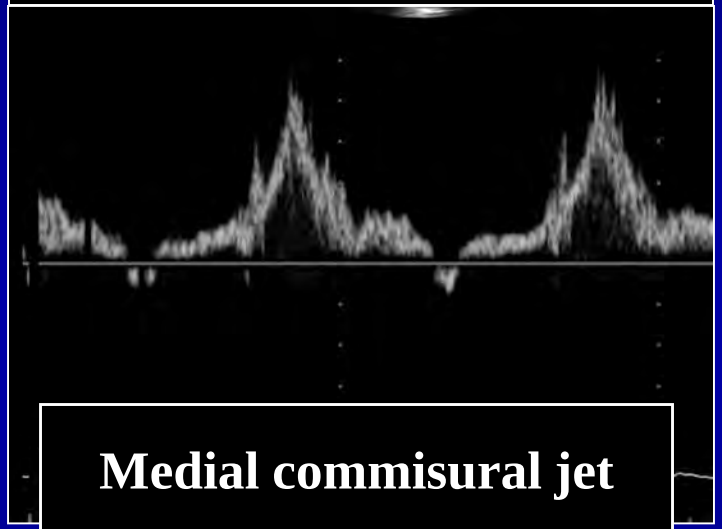
Flail of medial P3



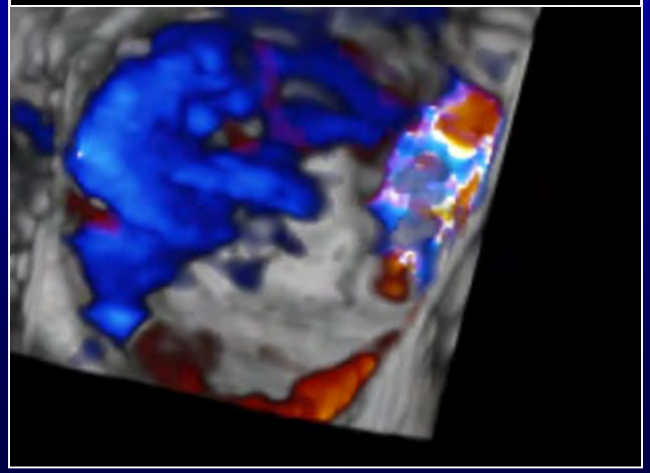
Severe MR due to a medial commissural jet



D-dominant pulmonary vein flow

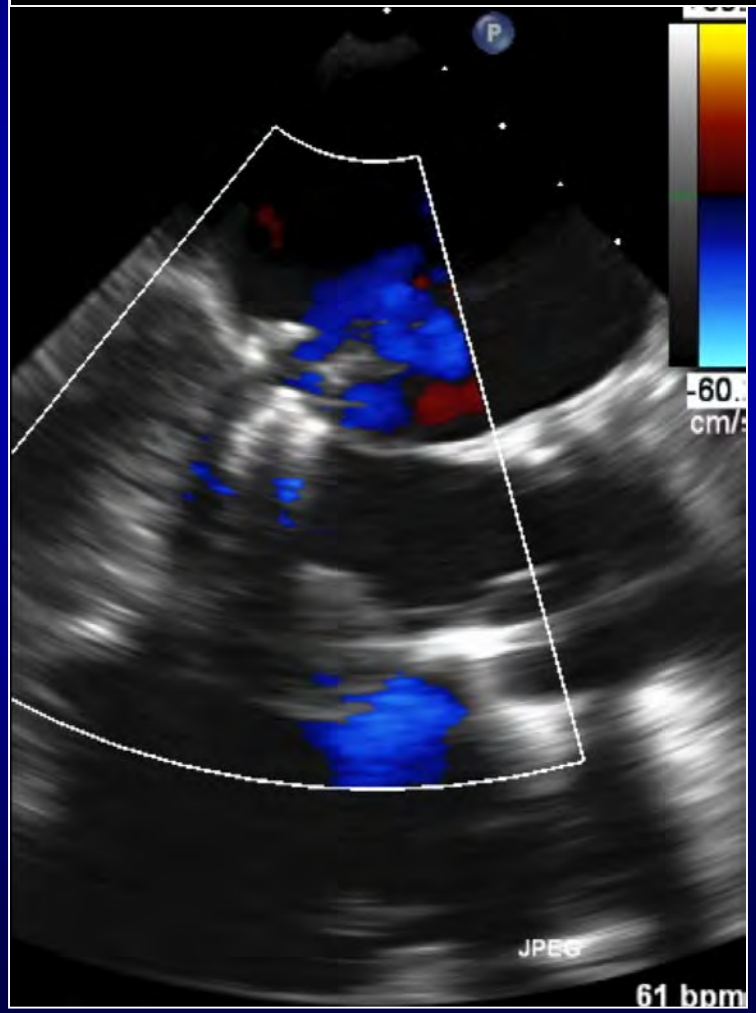


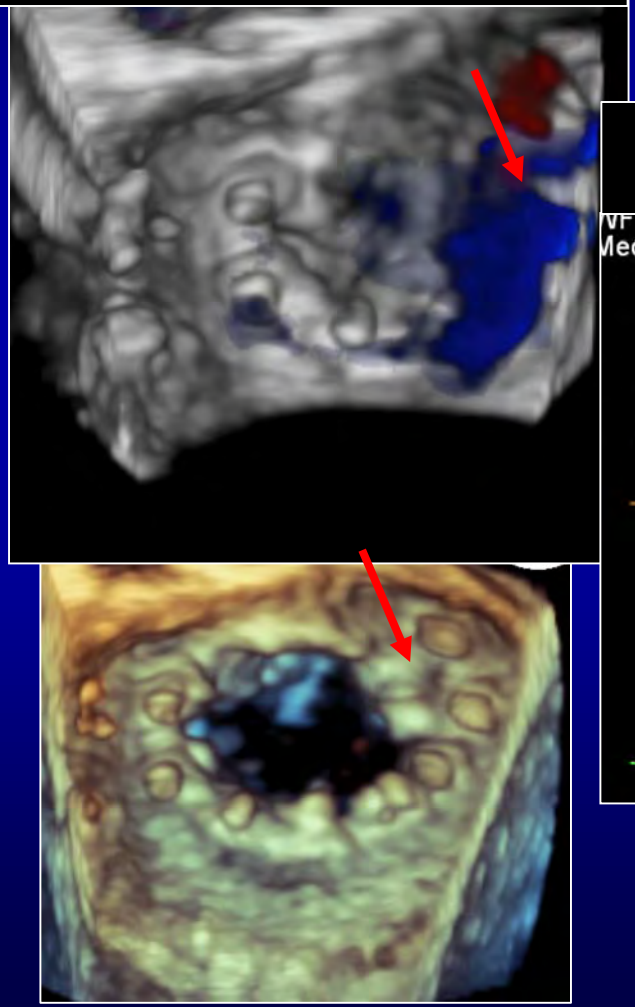
Medial commisural jet



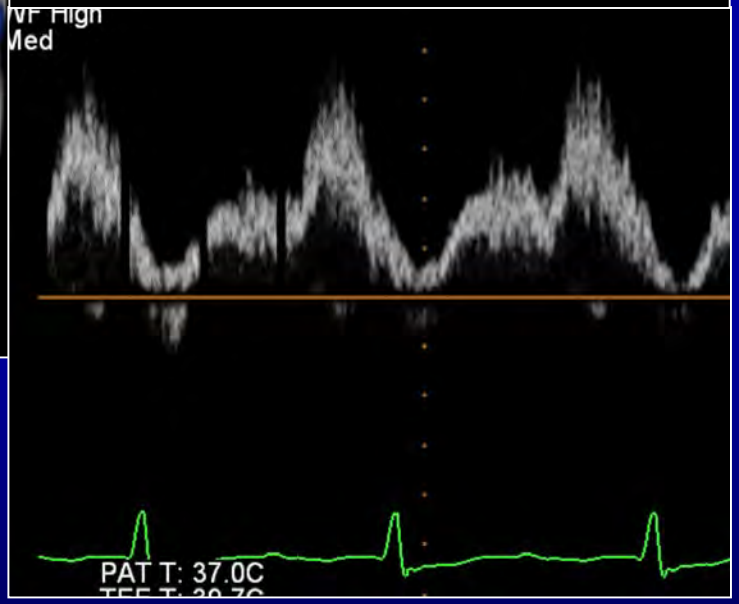
s/p transcatheter mitral valve repair with MitraClip x 1 at the medial commissure

Trivial residual MR



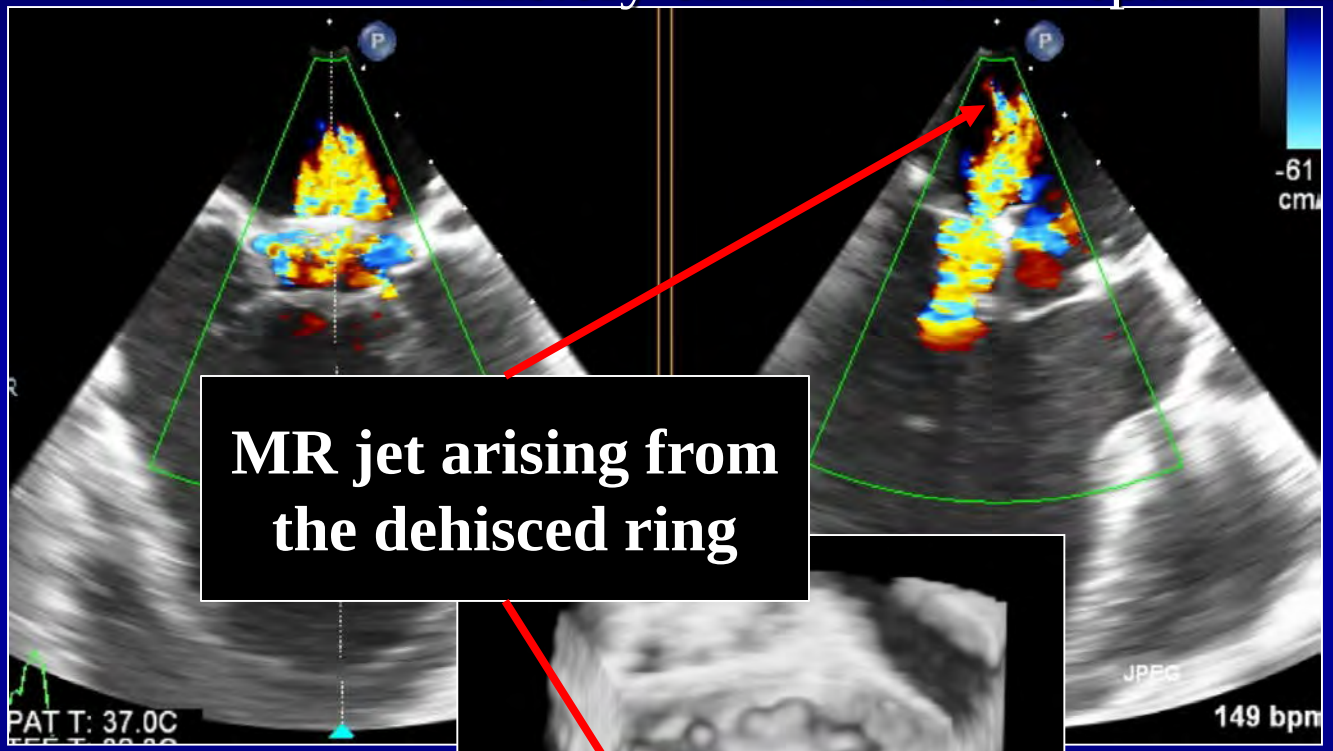


D-dominant pulmonary vein flow



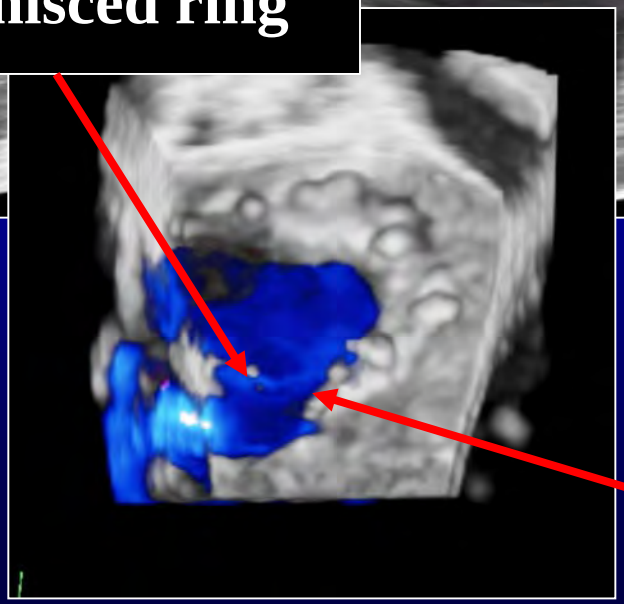
84 y/o male with EF 20% in cardiogenic shock, acute renal failure and recurrent VT

History of mitral valve repair with a mitral ring



MR jet arising from the dehisced ring

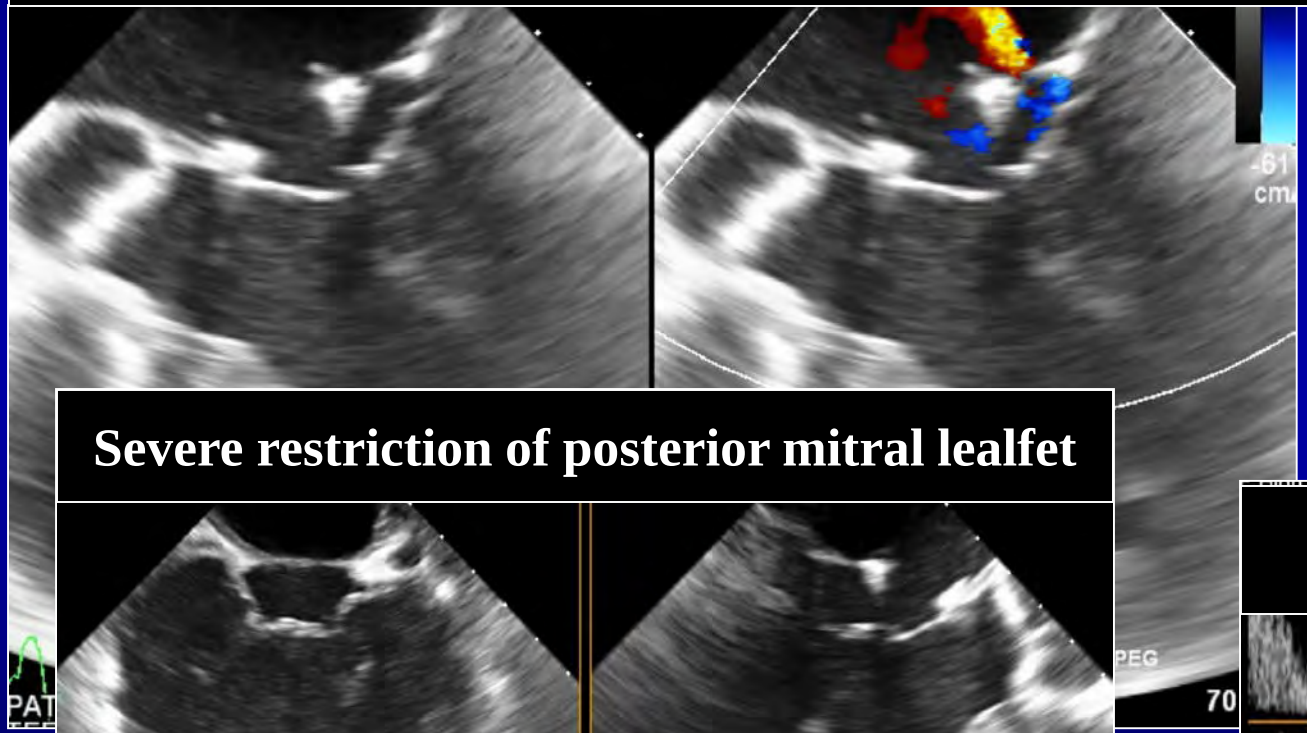
Initial TEE assessment revealed dehisced mitral valve ring, with concern for severe MR originating from the site of ring dehiscence

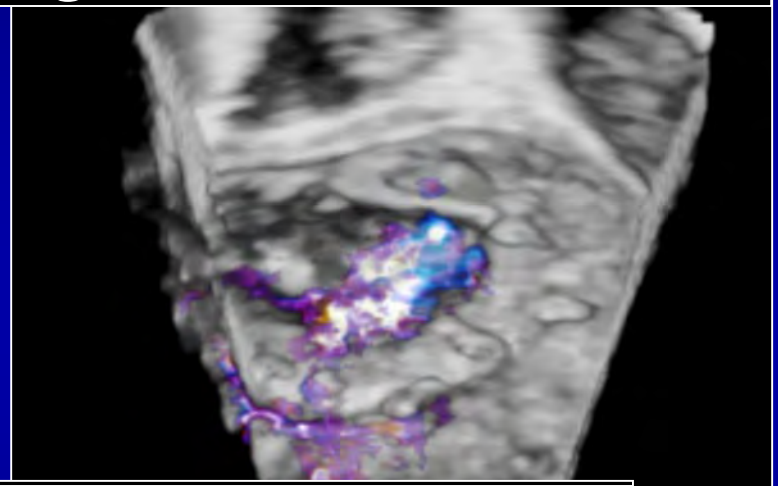


Dehisced ring

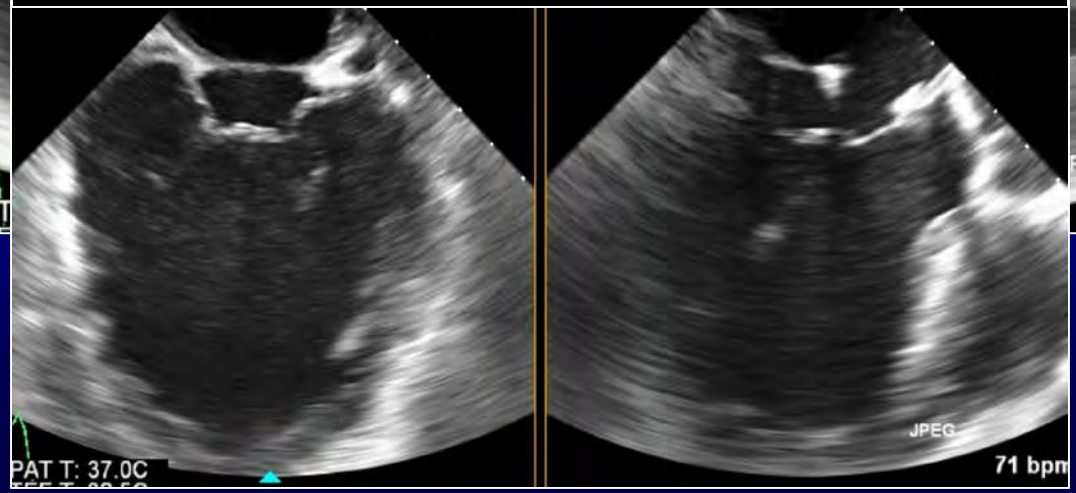
Further TEE evaluation revealed the MR jet originating from the mitral valve leaflets

Very severe MR originating from the mitral valve leaflets and directed towards the dehisced ring

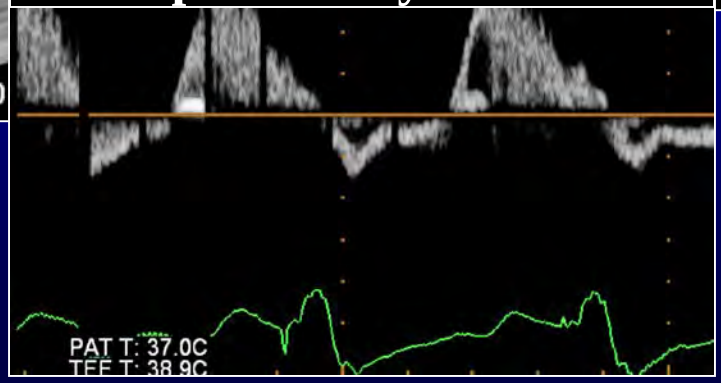




Severe restriction of posterior mitral lealfet

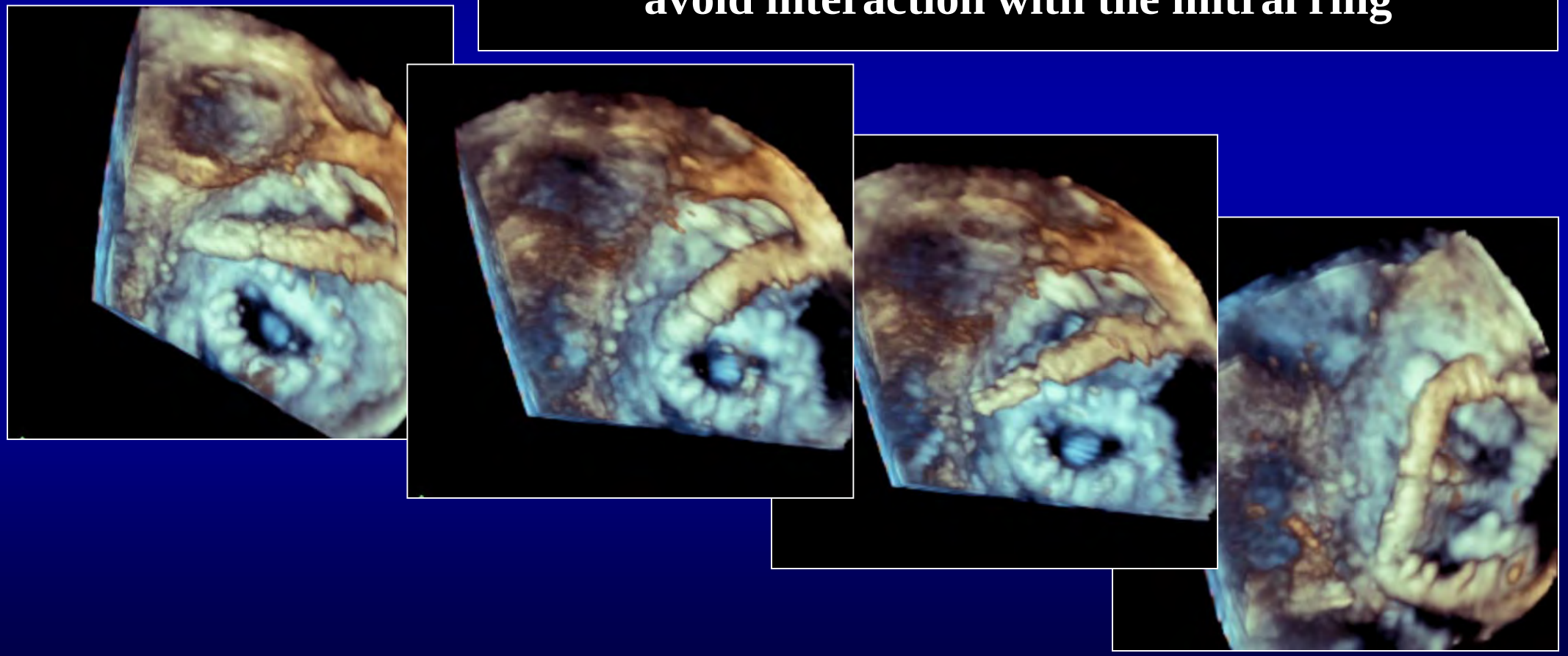


Systolic flow reversal in pulmonary veins

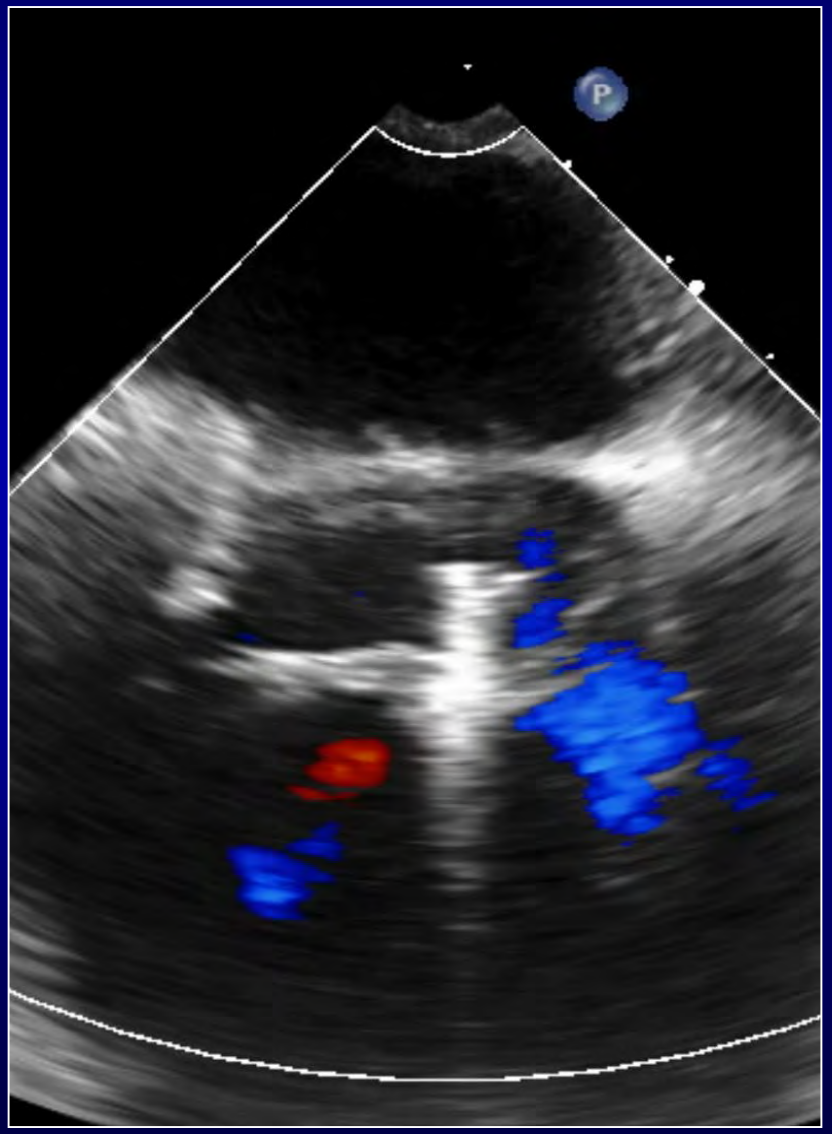


Patient brought to the cath lab for emergent MitraClip procedure, on 2 inotropes

Careful steering of the MitraClip delivery system to avoid interaction with the mitral ring



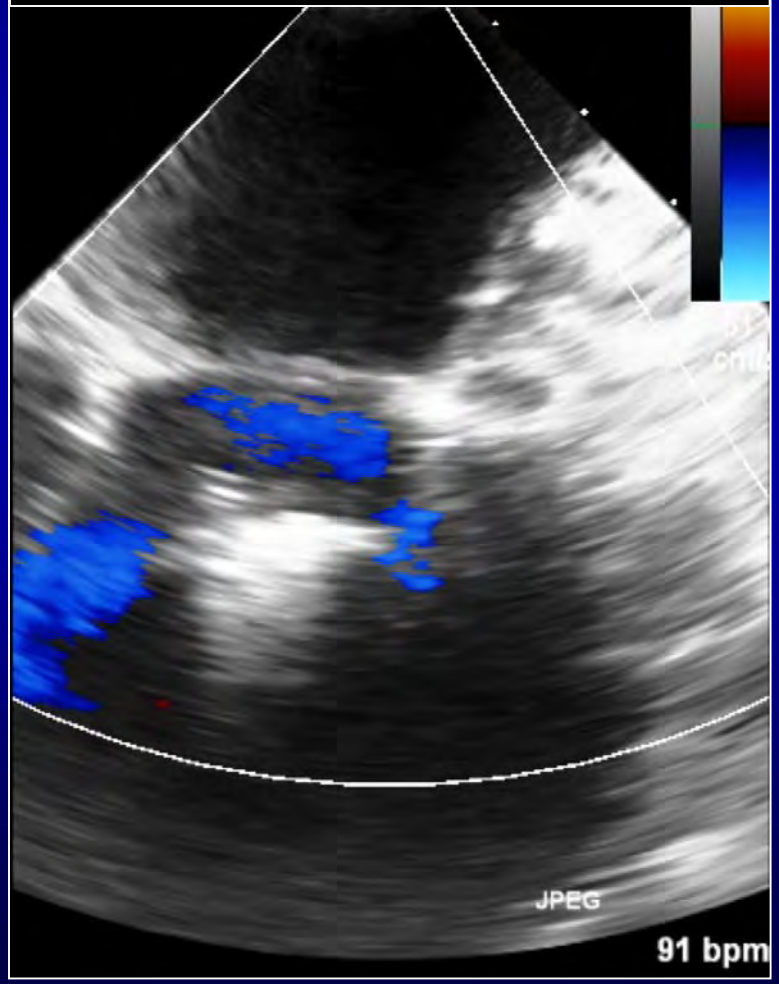
Moderate residual MR after MitraClip x 1



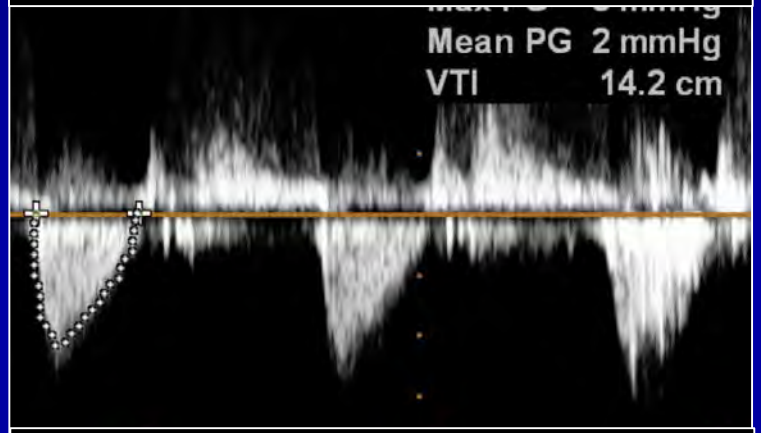
Final result s/p MitraClip x 2

Creatinine improved from 2.1 to 1.4; VT resolved, inotropes discontinued, patient discharged to home on POD# 4

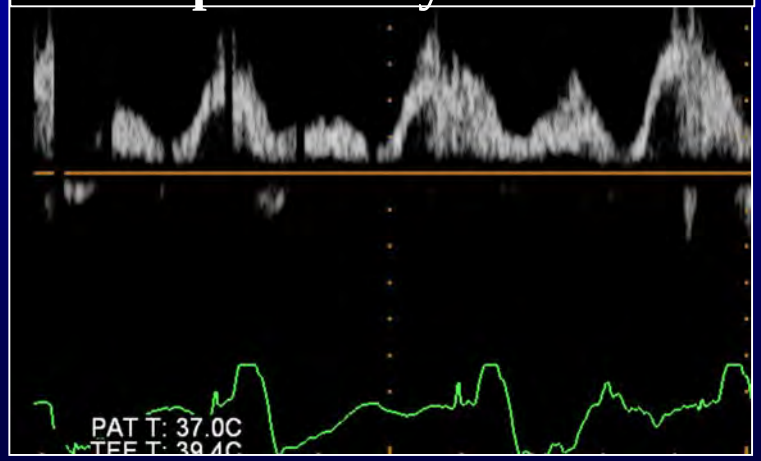
Mild residual MR



Mitral valve gradient 2mmHg



No systolic flow reversal in pulmonary veins



Expanded indications of the MitraClip: Beyond the A2/P2 EVEREST criteria

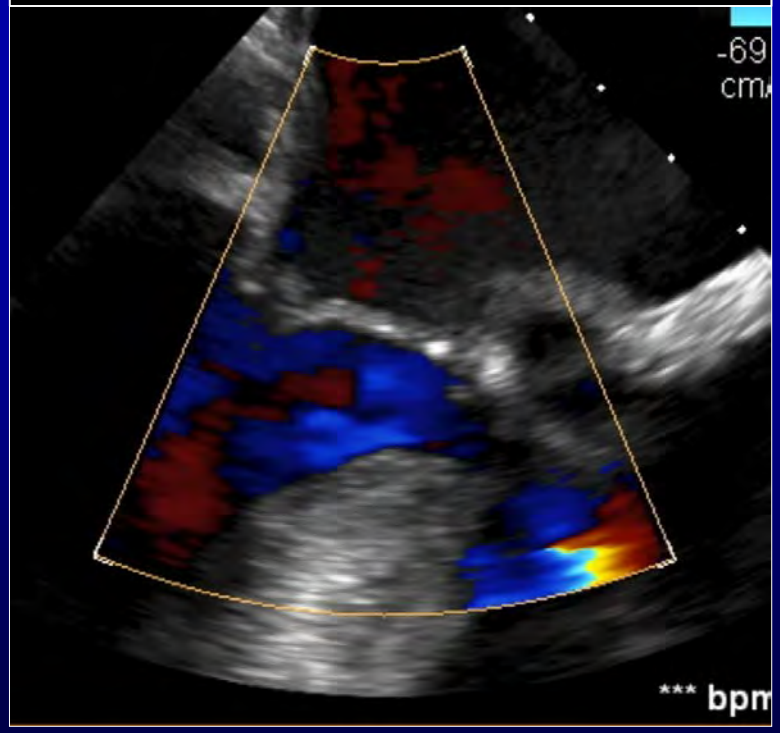
- A1P1 or A3P3 flail or prolapse
- Failed surgical repair
  - Ring annuloplasty or snapping of artificial chord
- Severe MR due to septal anterior motion in HOCM
- Post-MI Ruptured papillary muscle

89 y/o female presenting with shortness of breath

SAM, LVOT obstruction and severe MR

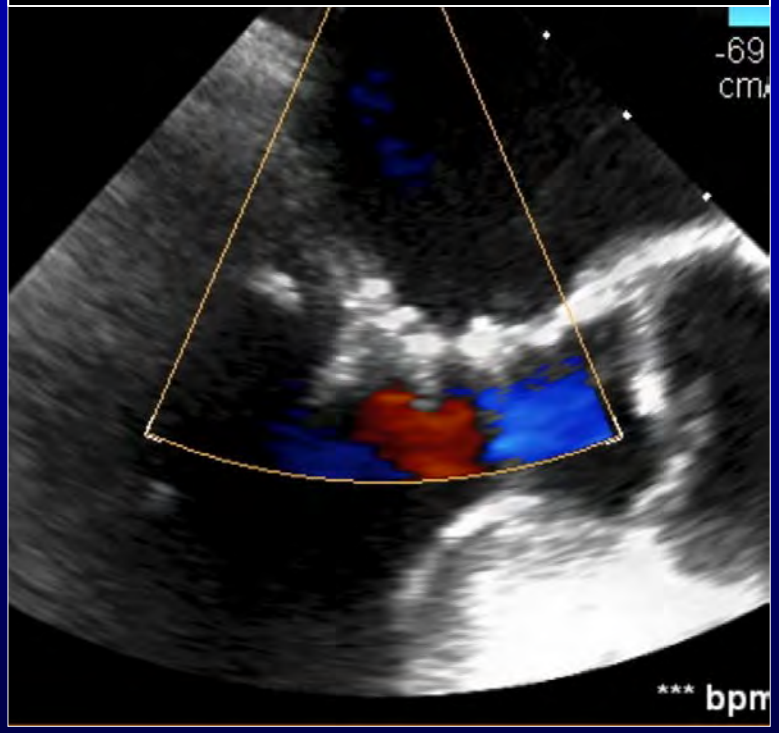
Baseline

SAM, LVOT obstruction and severe MR



s/p MitraClip x 1

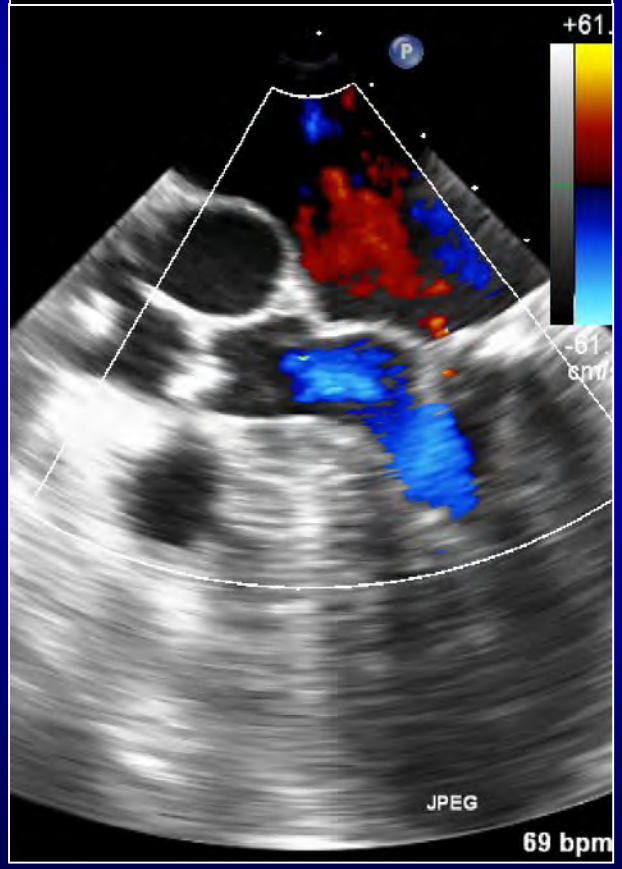
Trivial MR, no LVOT obstruction



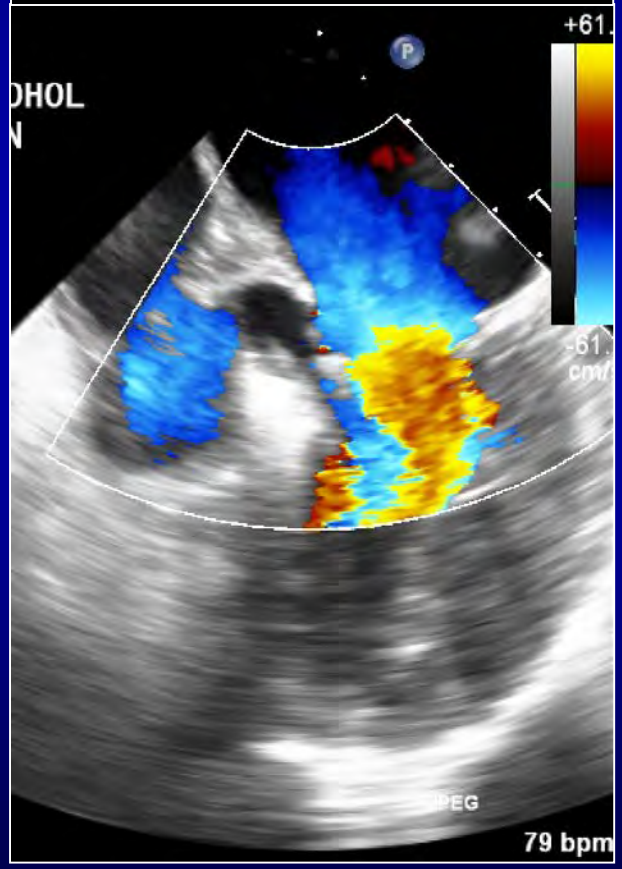
91 y/o female with severe MR referred for MitraClip

TEE revealed SAM with severe MR and LVOT gradient

Baseline
Severe MR



s/p alcohol septal ablation: Mild MR



Alcohol septal ablation performed instead of MitraClip, with successful resolution of MR and LVOT gradient

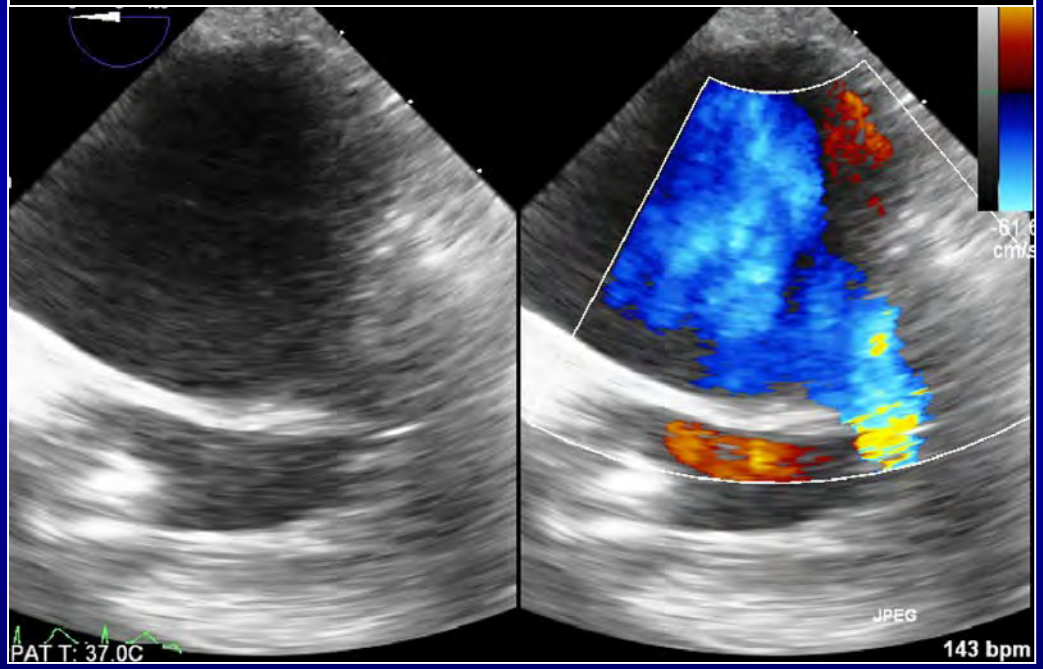
Expanded indications of the MitraClip: Beyond the A2/P2 EVEREST criteria

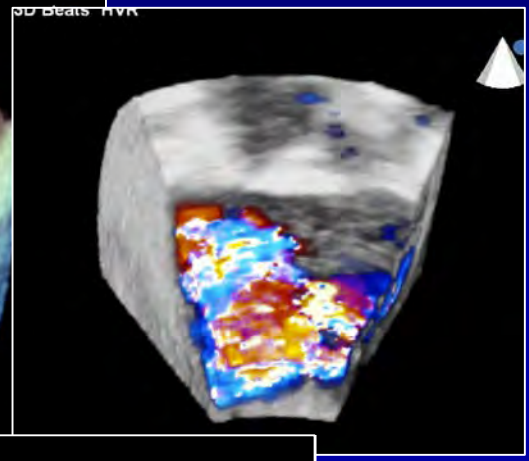
- A1P1 or A3P3 flail or prolapse
- Failed surgical repair
  - Ring annuloplasty or snapping of artificial chord
- Severe MR due to septal anterior motion in HOCM
- Post-MI Ruptured papillary muscle

81 y/o female s/p multivessel PCI for STEMI

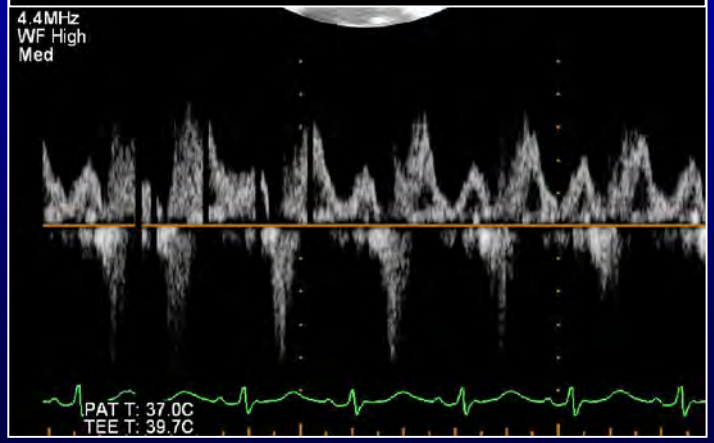
Transferred to Cedars-Sinai, in cardiogenic shock, for MitraClip for ruptured papillary muscle

Ruptured papillary muscle with torrential MR

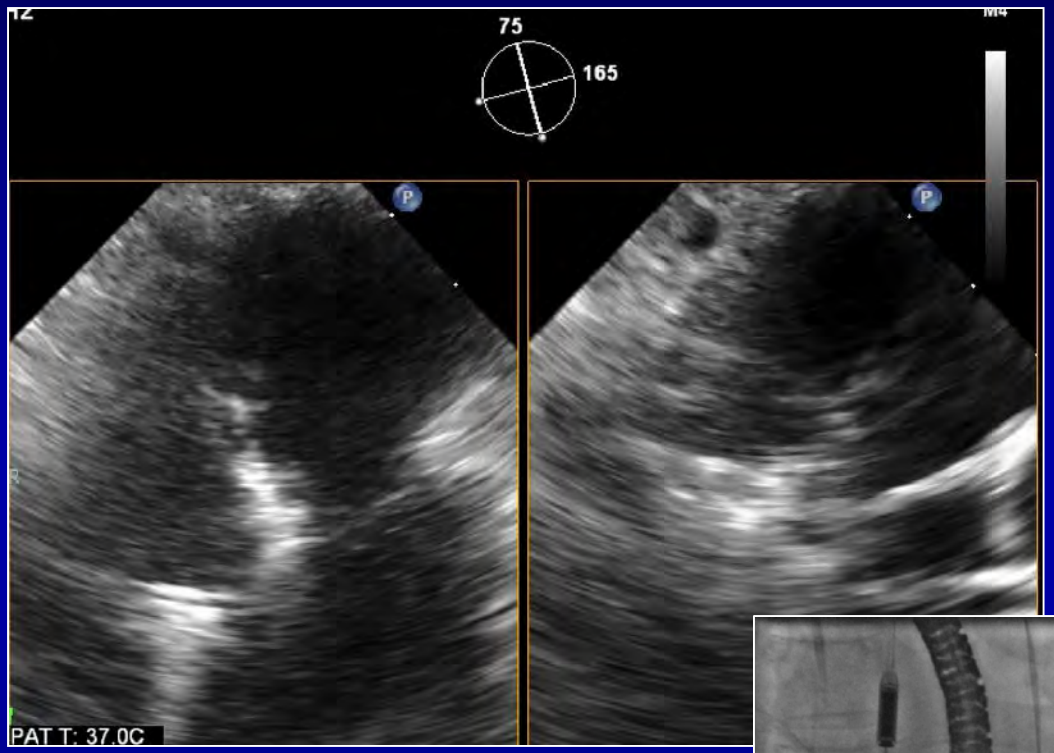


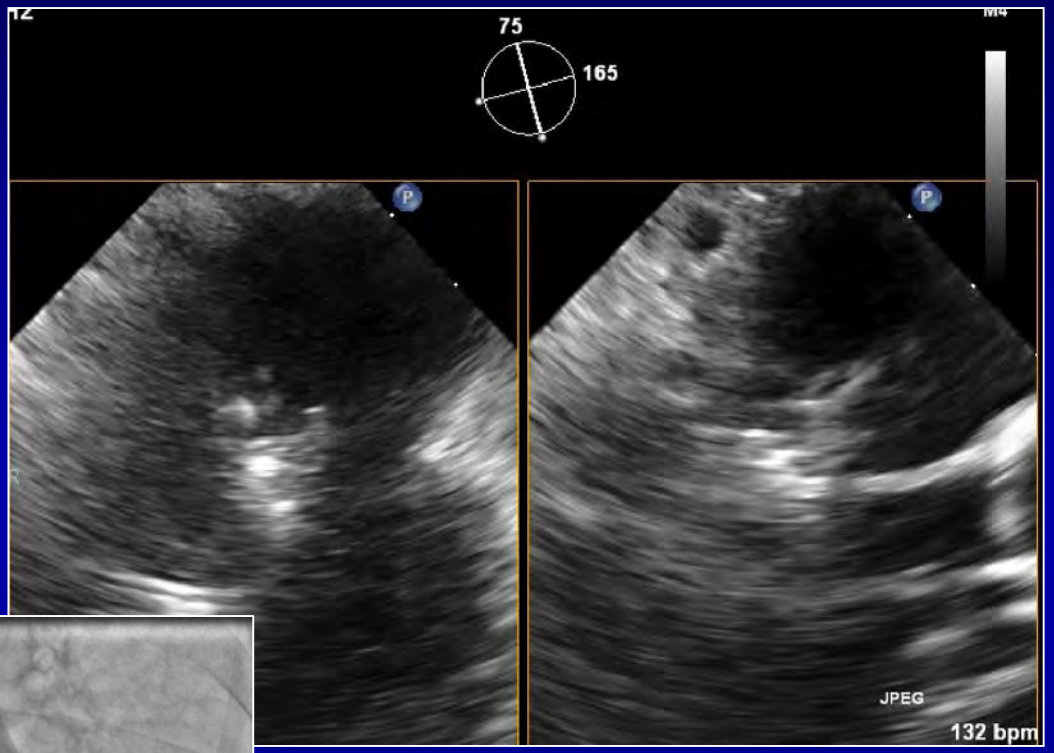


Systolic pulmonary vein flow reversal

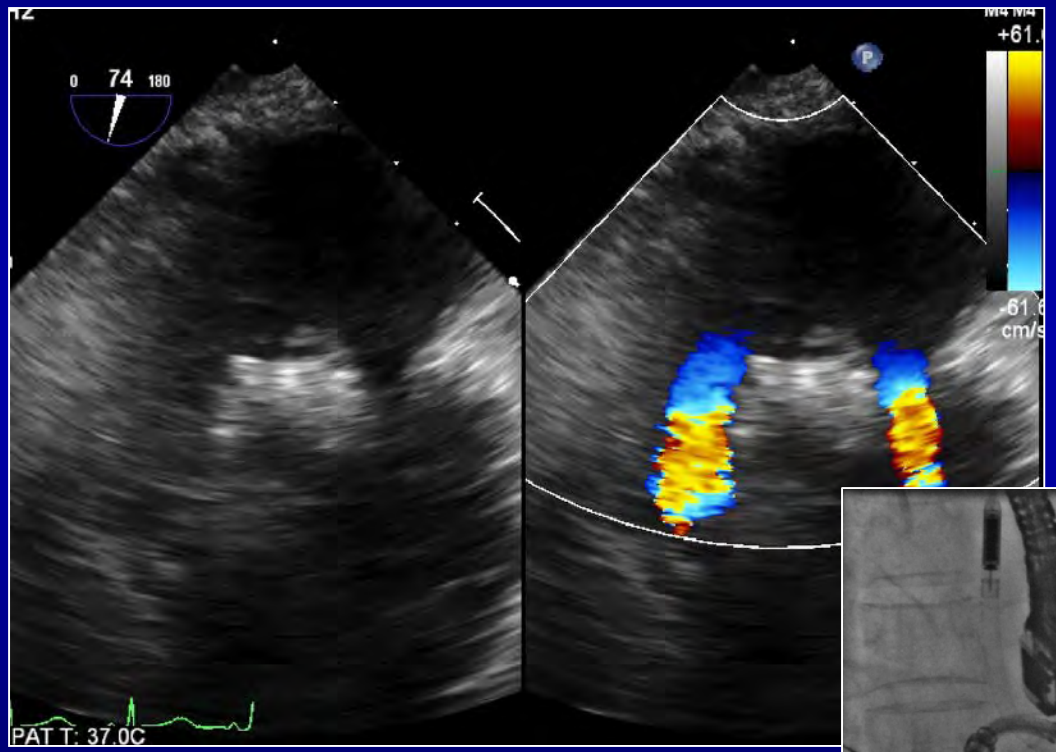


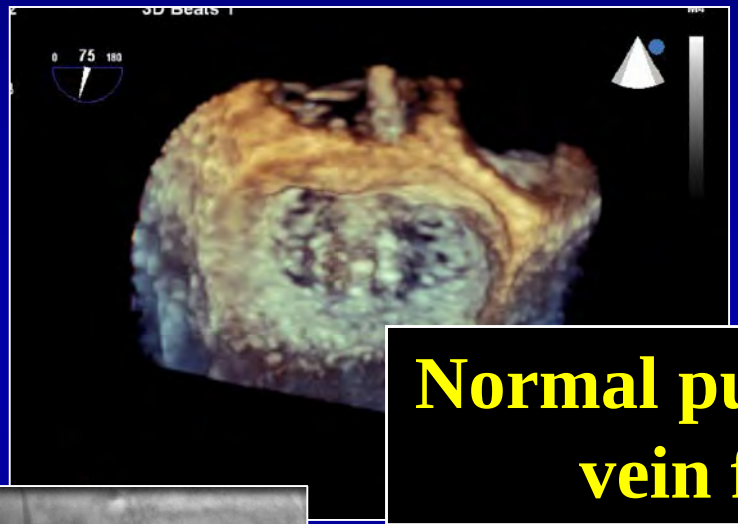
Ruptured papillary muscle grasped with the 1st Clip



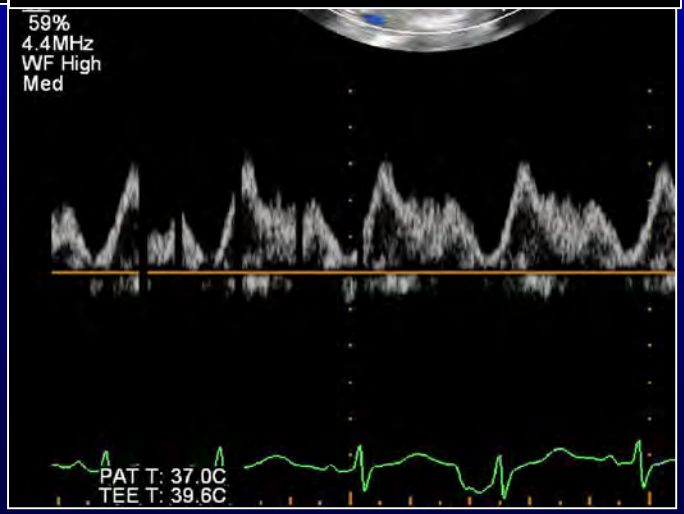


2 additional clips placed to stabilize the 1st clip
Mild MR s/p 3 Clips for ruptured papillary muscle





Normal pulmonary vein flow



Transcatheter treatment of functional MR

Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation

Obadia J-F. et al. NEJM 2018
MITRA FR trial

Transcatheter Mitral-Valve Repair in Patients with Heart Failure

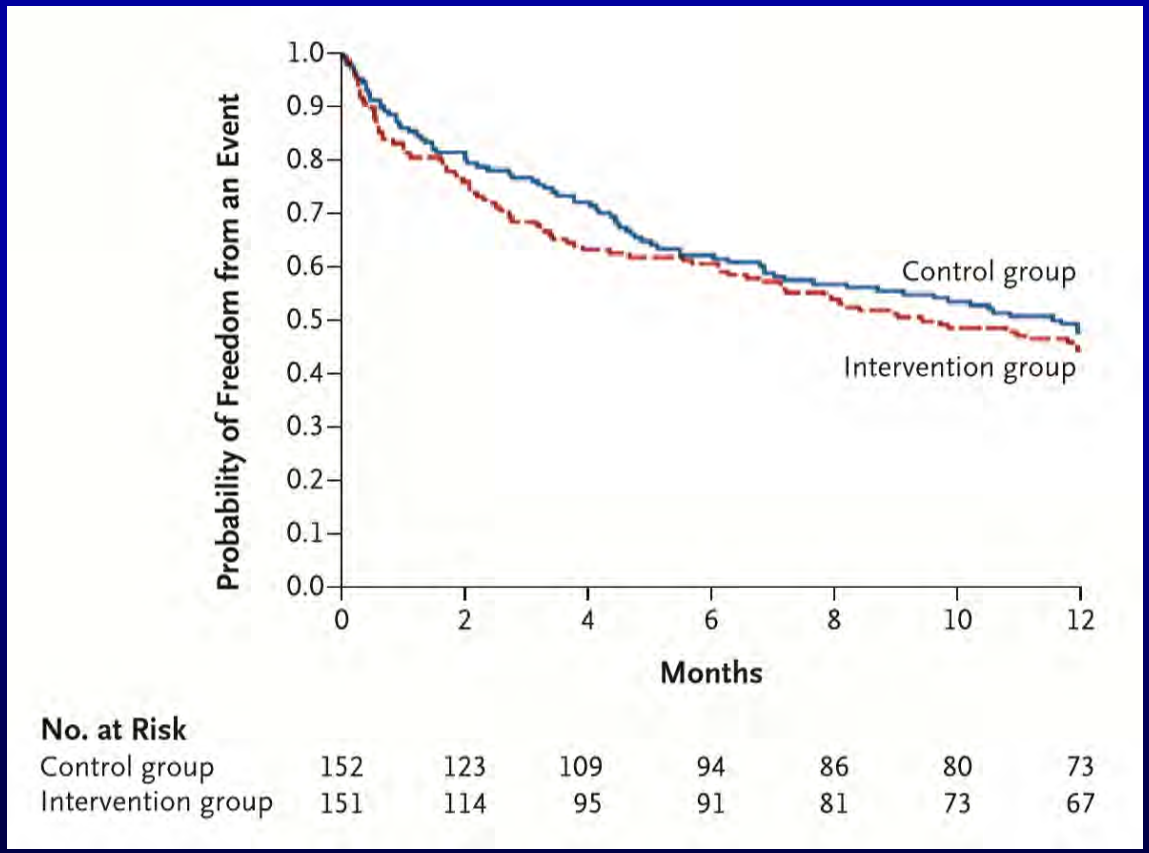
Stone G. et al. NEJM 2018
COAPT trial

Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation

J.-F. Obadia, D. Messika-Zeitoun, G. Leurent, B. Iung, G. Bonnet, N. Piriou, T. Lefèvre, C. Piot, F. Rouleau, D. Carrié, M. Nejjari, P. Ohlmann, F. Leclercq, C. Saint Etienne, E. Teiger, L. Leroux, N. Karam, N. Michel, M. Gilard, E. Donal, J.-N. Trochu, B. Cormier, X. Armoiry, F. Boutitie, D. Maucort-Boulch, C. Barnel, G. Samson, P. Guerin, A. Vahanian, and N. Mewton, for the MITRA-FR Investigators*

MITRA-FR trial: 304 patients with moderate or severe functional MR

- MitraClip: 152
- Medical therapy: 152



No difference in mortality or heart failure hospitalization at 1 year

Obadia J-F. et al. NEJM 2018

Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation

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MITRA-FR trial: 304 patients with moderate or severe functional MR

- MitraClip: 152
- Medical therapy: 152

No difference in individual end-points of death or heart failure hospitalization

Outcome	Intervention Group (N=152)	Control Group (N=152)	Hazard Ratio or Odds Ratio (95% CI)*	P Value†
Composite primary outcome: death from any cause or unplanned hospitalization for heart failure at 12 months — no. (%)	83 (54.6)	78 (51.3)	1.16 (0.73–1.84)	0.53
Secondary outcomes‡				
Death from any cause	37 (24.3)	34 (22.4)	1.11 (0.69–1.77)	
Cardiovascular death	33 (21.7)	31 (20.4)	1.09 (0.67–1.78)	
Unplanned hospitalization for heart failure	74 (48.7)	72 (47.4)	1.13 (0.81–1.56)	
Major adverse cardiovascular events§	86 (56.6)	78 (51.3)	1.22 (0.89–1.66)	

Obadia J-F. et al. NEJM 2018

Transcatheter Mitral-Valve Repair in Patients with Heart Failure

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

COAPT trial: 614 patients with moderate-severe/severe functional MR

- MitraClip: 312
- Medical therapy: 302

COAPT TRIAL

The COAPT Trial

Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation

A parallel-controlled, open-label, multicenter trial in ~610 patients with heart failure and moderate-to-severe (3+) or severe (4+) secondary MR who remained symptomatic despite maximally-tolerated GDMT

Randomize 1:1*

MitraClip + GDMT
N=312

GDMT alone
N=302

Stone G. et al. NEJM 2018

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COAPT trial: 610 patients with moderate-severe/severe functional MR

- MitraClip: 305
- Medical therapy: 305

Key inclusion criteria

- Ischemic or non-ischemic cardiomyopathy with **LVEF 20%-50%** and LVESD ≤70 mm
- **Moderate-to-severe (3+) or severe (4+) secondary MR** confirmed by an independent echo core laboratory prior to enrollment (US ASE criteria)
- NYHA functional class II-IVa (ambulatory) despite a stable maximally-tolerated GDMT regimen and CRT (if appropriate) per societal guidelines
- Pt has had **at least one HF hospitalization within 12 months and/or a BNP ≥300 pg/ml* or a NT-proBNP ≥1500 pg/ml***
- Not appropriate for mitral valve surgery by local heart team assessment
- IC believes secondary MR can be successfully treated by the MitraClip

Stone G. et al. NEJM 2018

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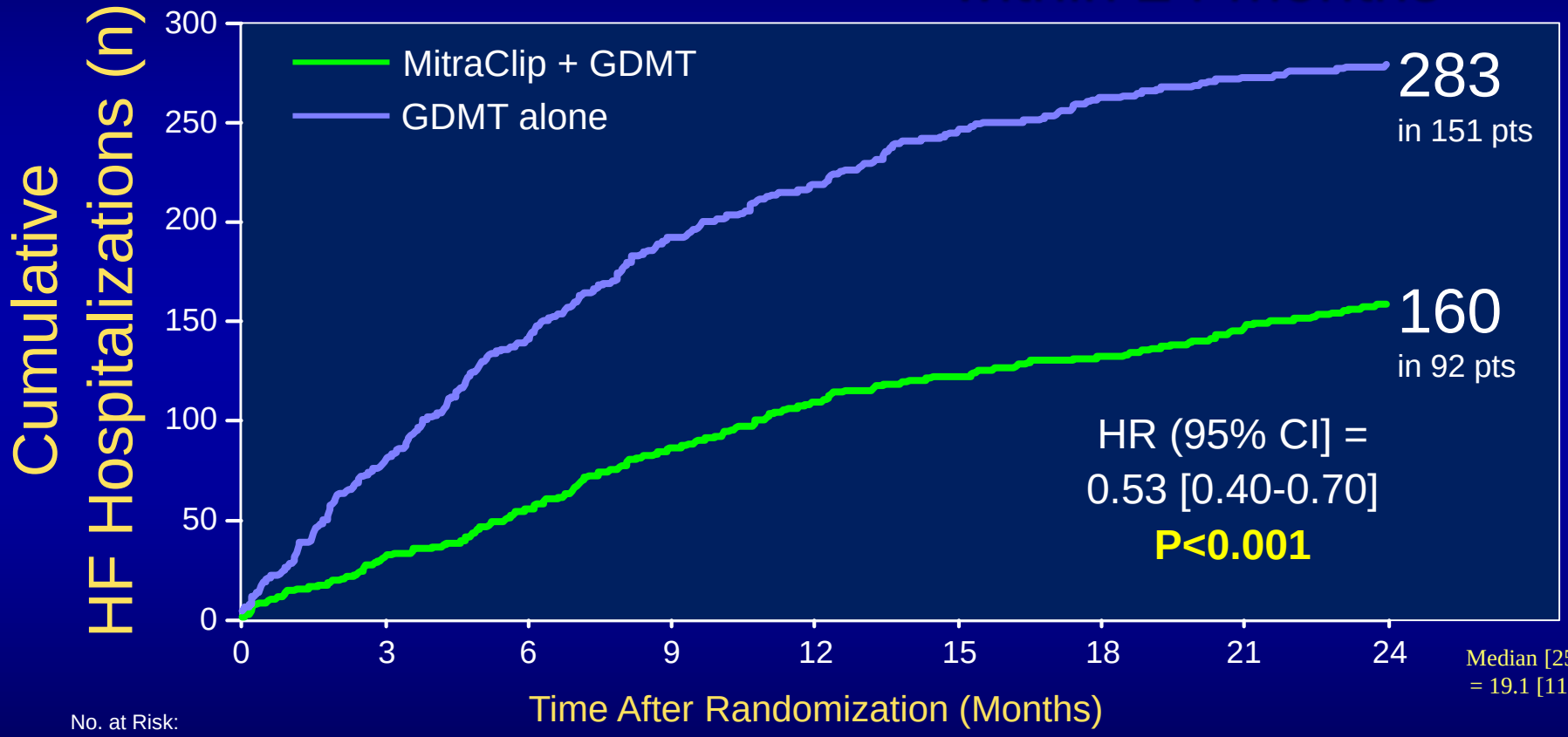
Primary Effectiveness Endpoint

All Hospitalizations for HF within 24 months



Median [25%, 75%] FU = 19.1 [11.9, 24.0] mos

No. at Risk:

MitraClip	302	286	269	253	236	191	178	161	124
GDMT	312	294	271	245	219	176	145	121	88

Stone G. et al. NEJM 2018

Transcatheter Mitral-Valve Repair in Patients with Heart Failure

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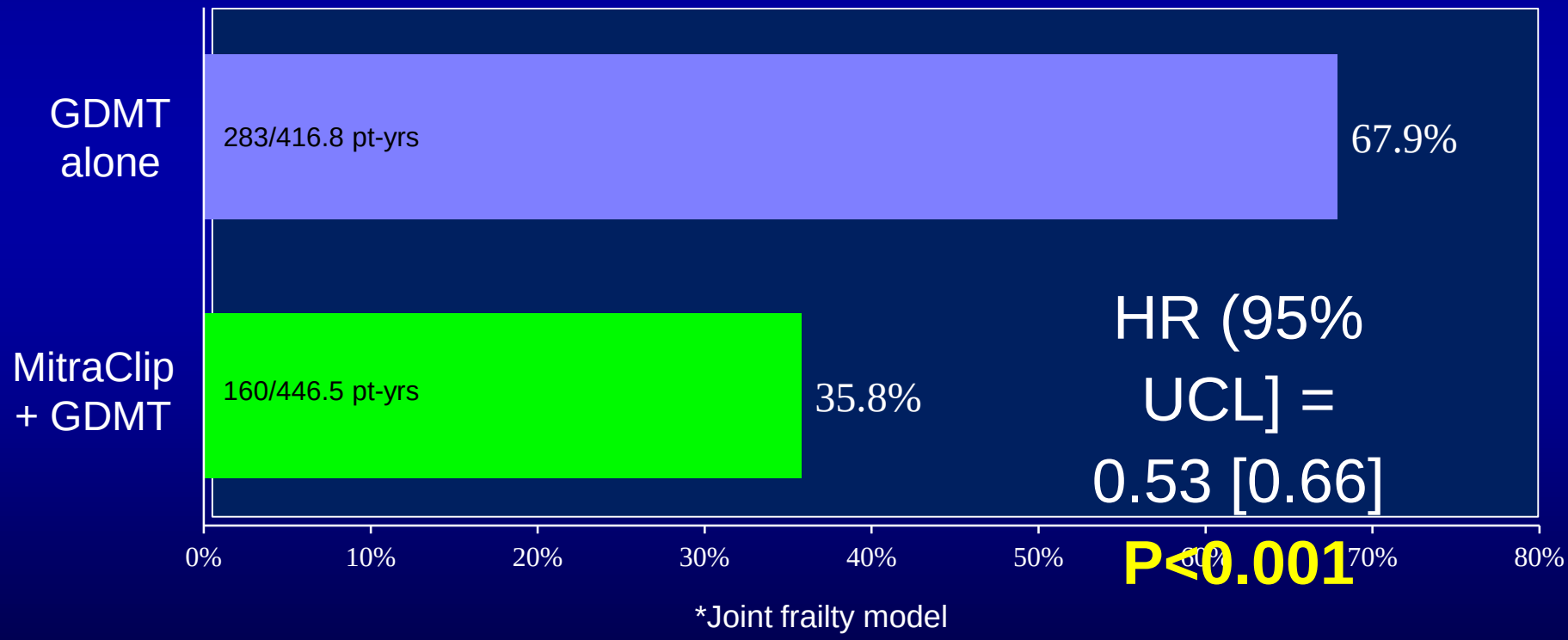
Primary Effectiveness Endpoint

Hospitalizations for HF within 24 months

Annualized rates of HF hospitalization*

NNT (24 mo) = 3.1 [95% CI 1.9, 8.2]



*Joint frailty model

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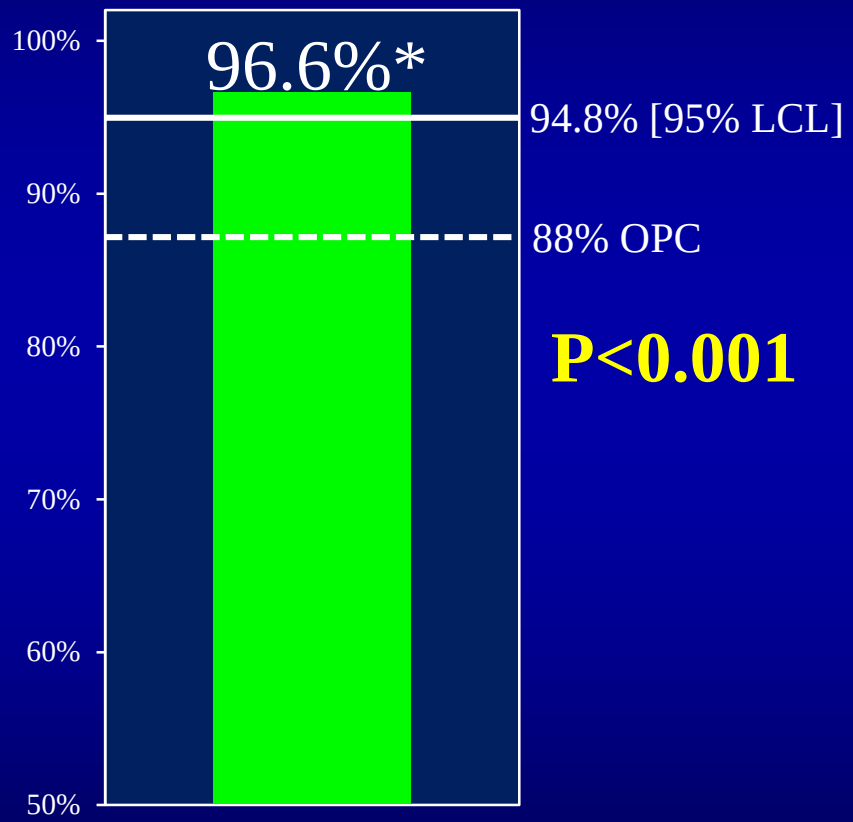
Primary Safety Endpoint

Freedom from Device-related Complications within 12 months



MitraClip procedure attempted	N=293
Device-related complications	9 (3.4%)
- Single leaflet device attachment	2 (0.7%)
- Device embolization	1 (0.3%)
- Endocarditis requiring surgery	0 (0.0%)
- Mitral stenosis requiring surgery	0 (0.0%)
- Left ventricular assist device implant	3 (1.2%)
- Heart transplant	2 (0.8%)
- Any device-related complication requiring non-elective CV surgery	1 (0.3%)

*KM estimate; **Calculated from Z test with Greenwood's method of estimated variance against a pre-specified objective performance goal of 88%

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Powered Secondary Endpoints

- Tested in hierarchical order[1] -

	P-value
1. MR grade ≤2+ at 12 months	
2. All-cause mortality at 12 months[2]	
3. Death and all HF hospitalization through 24 months (Finkelstein-Schoenfeld)	
4. Change in QOL (KCCQ) from baseline to 12 months	
5. Change in 6MWD from baseline to 12 months	
6. All-cause hospitalizations through 24 months	
7. NYHA class I or II at 12 months	
8. Change in LVEDV from baseline to 12 months	
9. All-cause mortality at 24 months	
10. Death, stroke, MI, or non-elective CV surgery for device-related compls at 30 days[3]	

vs. the control group; *Powered for noninferiority against an objective performance goal

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Powered Secondary Endpoints

- Tested in hierarchical order[1] -

	P-value
1. MR grade ≤2+ at 12 months	<0.001
2. All-cause mortality at 12 months[2]	<0.001
3. Death and all HF hospitalization through 24 months (Finkelstein-Schoenfeld)	<0.001
4. Change in QOL (KCCQ) from baseline to 12 months	<0.001
5. Change in 6MWD from baseline to 12 months	<0.001
6. All-cause hospitalizations through 24 months	0.03
7. NYHA class I or II at 12 months	<0.001
8. Change in LVEDV from baseline to 12 months	0.003
9. All-cause mortality at 24 months	<0.001
10. Death, stroke, MI, or non-elective CV surgery for device-related compls at 30 days[3]	<0.001

[1]All powered for superiority unless otherwise noted; [2]Powered for noninferiority of the device vs. the control group; [3]Powered for noninferiority against an objective performance goal

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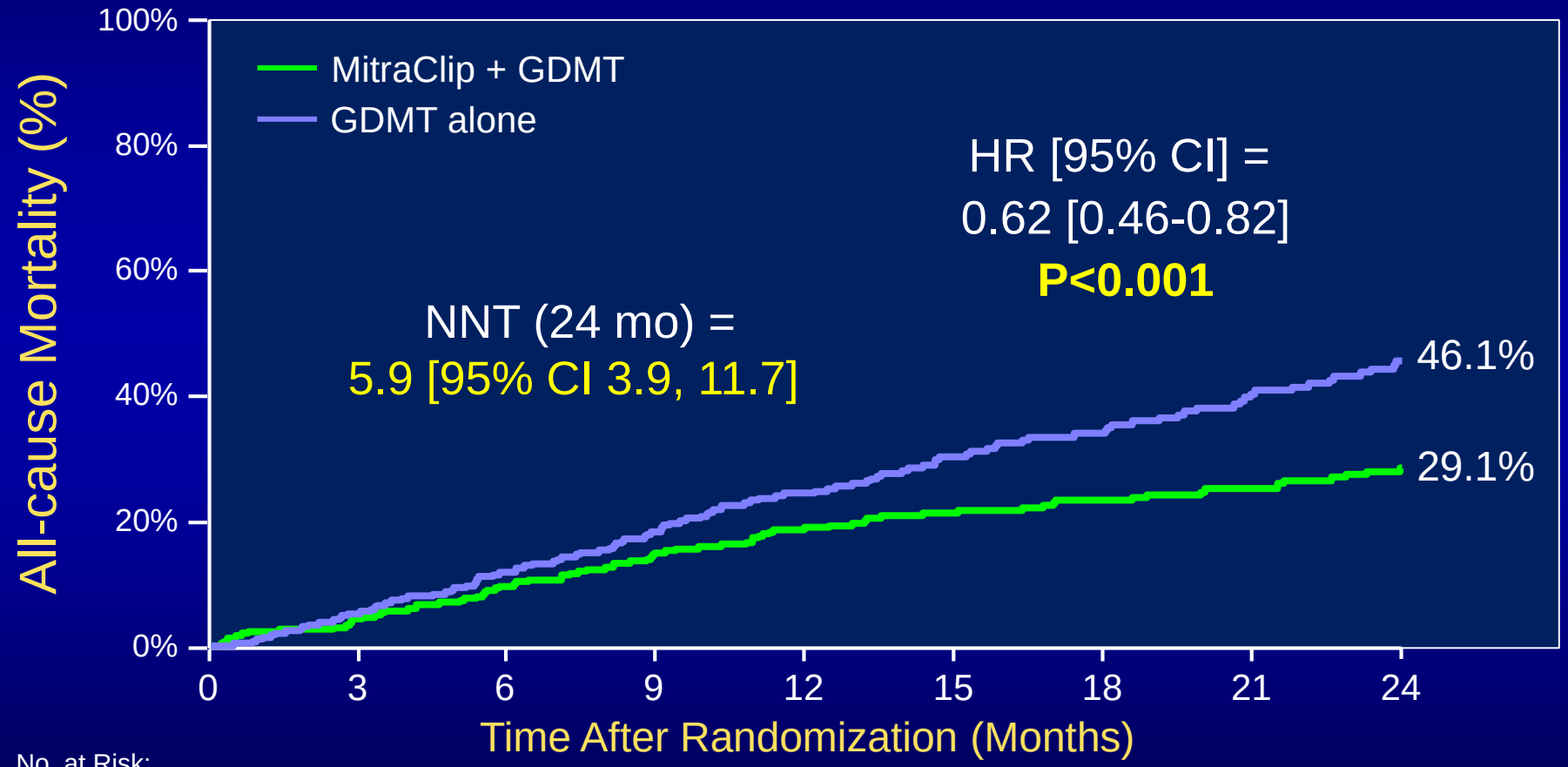
All-cause Mortality



No. at Risk:									
MitraClip + GDMT	302	286	269	253	236	191	178	161	124
GDMT alone	312	294	271	245	219	176	145	121	88

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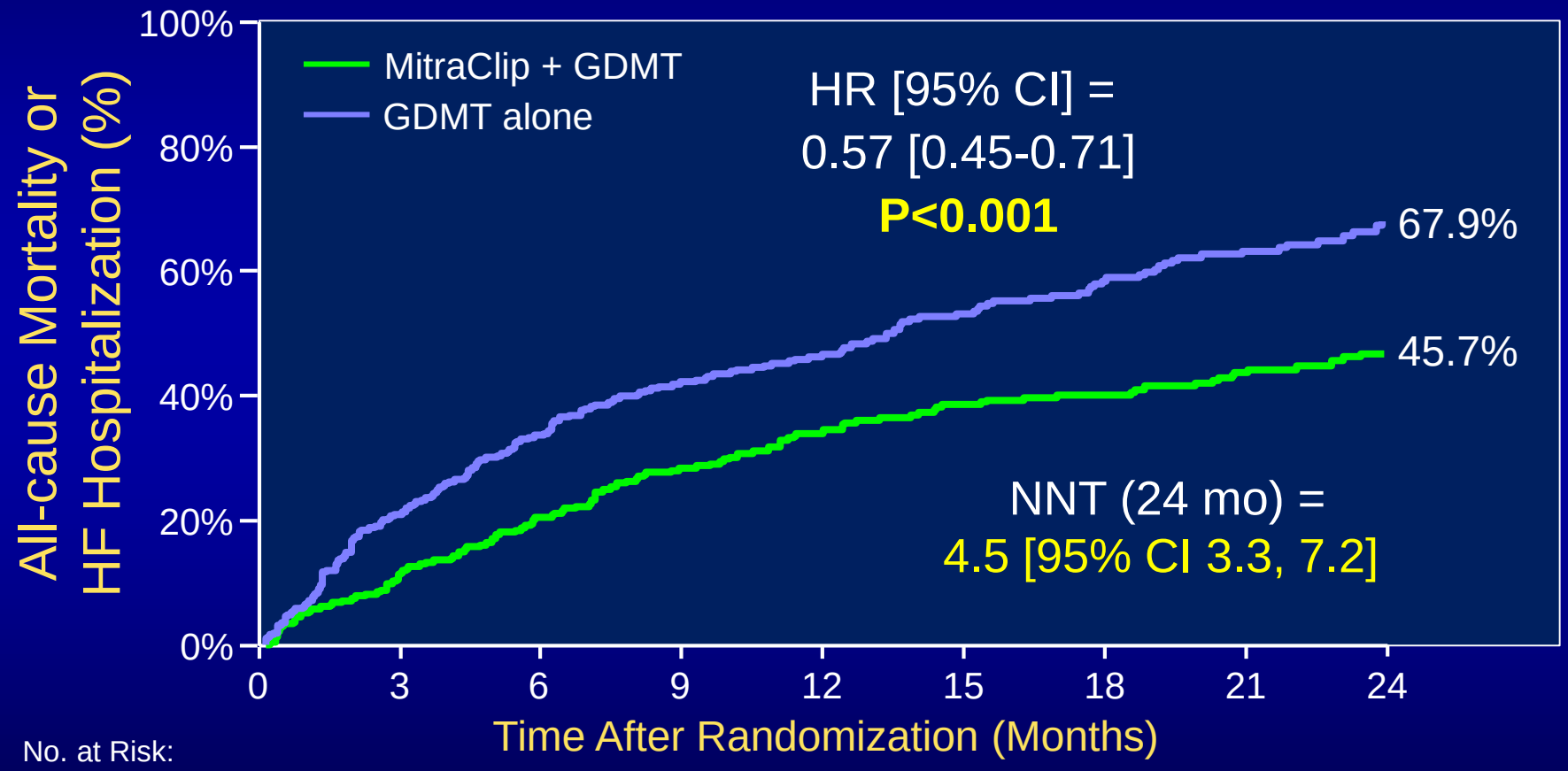
Death or HF Hospitalization



No. at Risk:

MitraClip + GDMT	302	264	238	215	194	154	145	126	97
GDMT alone	312	244	205	174	153	117	90	75	55

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24-Month Event Rates (ii)

	MitraClip + GDMT (n=302)	GDMT alone (n=312)	HR [95% CI]	P-value
MV intervention or surgery*	4.0%	9.0%	0.61 [0.27, 1.36]	0.23
- MitraClip	3.7%	6.6%	0.99 [0.38, 2.58]	0.99
- Mitral valve surgery	0.4%	2.5%	0.14 [0.02, 1.17]	0.07
PCI or CABG	2.8%	4.3%	0.62 [0.24, 1.60]	0.32
Stroke	4.4%	5.1%	0.96 [0.42, 2.22]	0.93
Myocardial infarction	4.7%	6.5%	0.82 [0.38, 1.78]	0.62
New CRT implant	2.9%	3.3%	0.85 [0.31, 2.34]	0.75
LVAD or heart transplant	4.4%	9.5%	0.37 [0.17, 0.81]	0.01
- LVAD	3.0%	7.1%	0.34 [0.13, 0.87]	0.02
- Heart transplant	1.4%	3.6%	0.35 [0.09, 1.32]	0.12

*Unplanned. Kaplan-Meier time-to-first event rates

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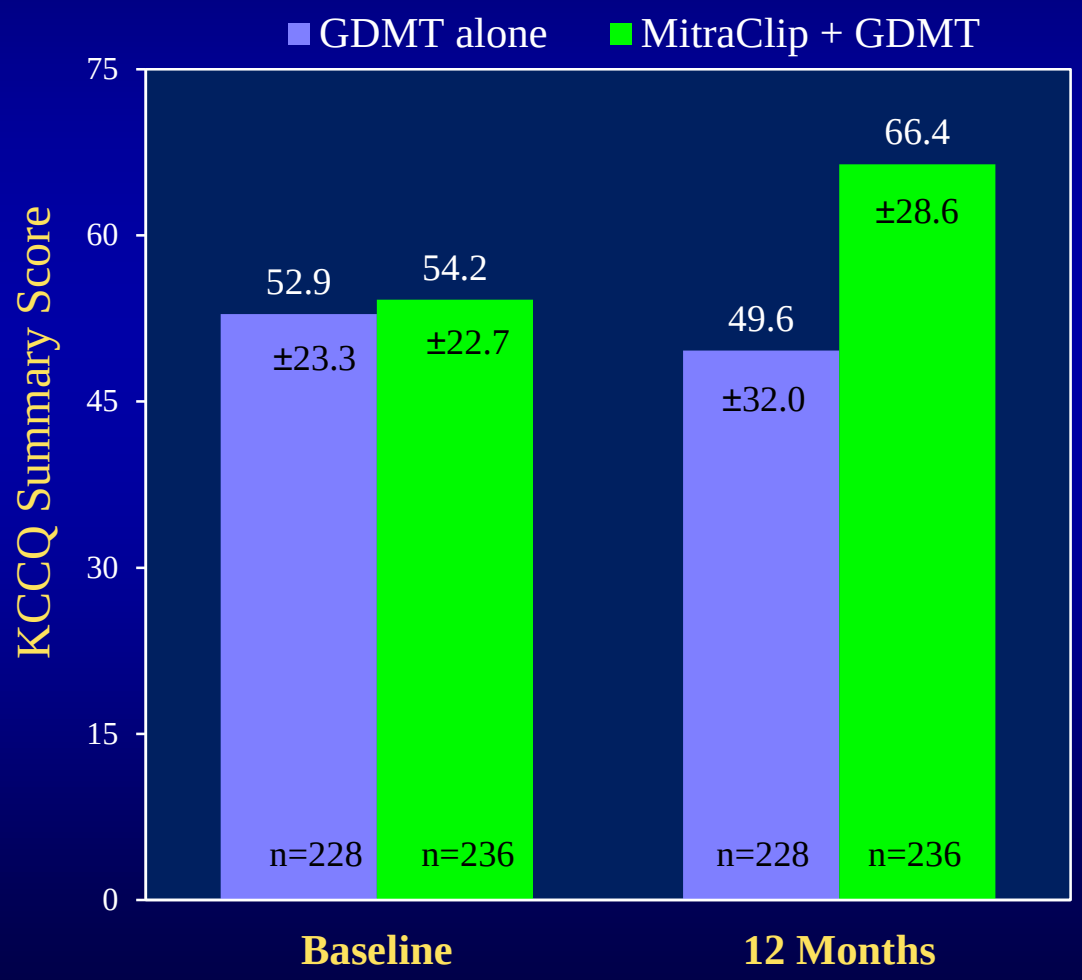
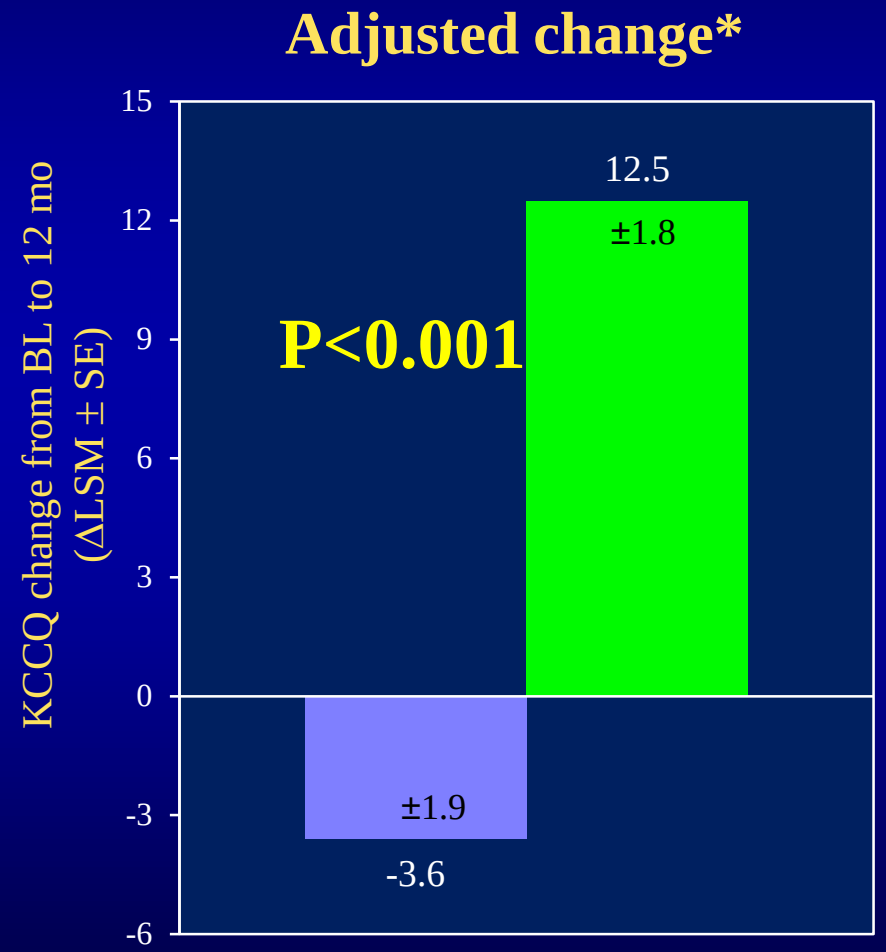
Change in KCCQ from Baseline to 12 Months





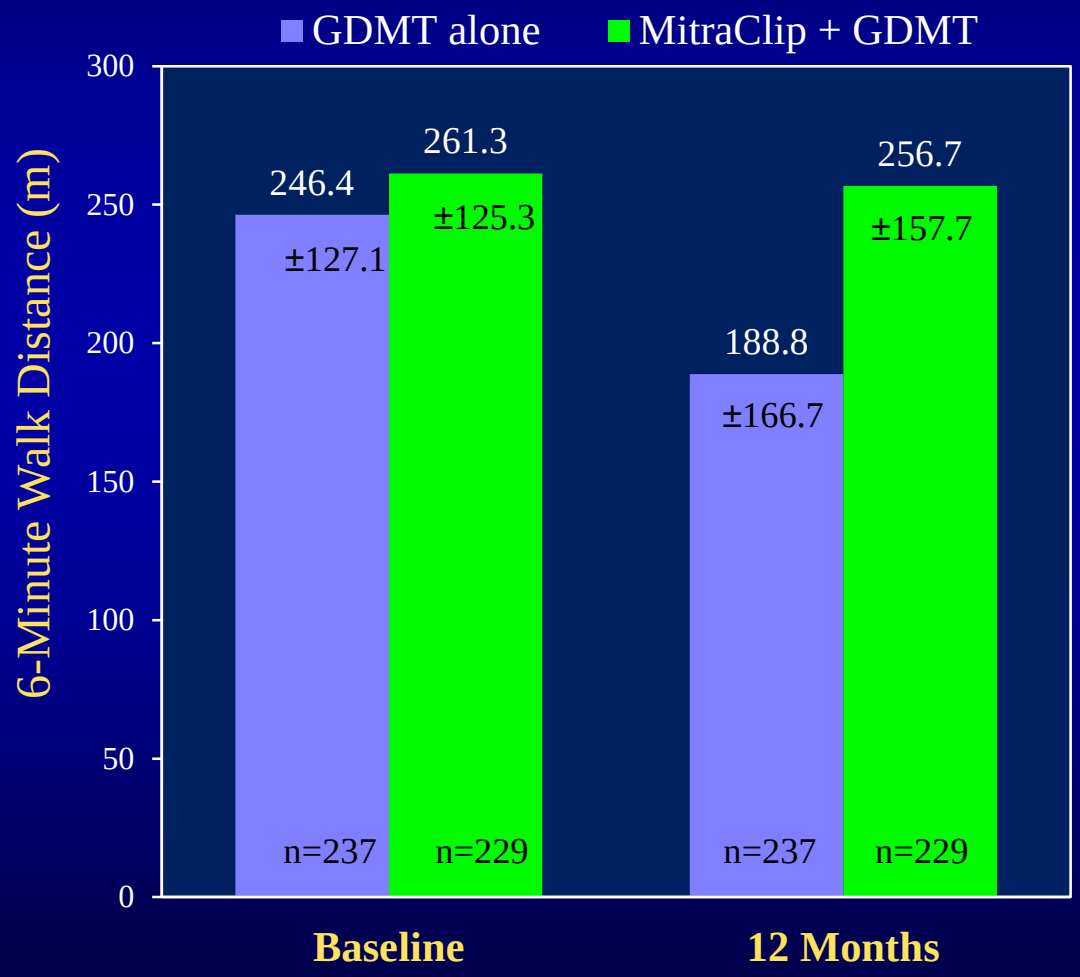
*Ancova

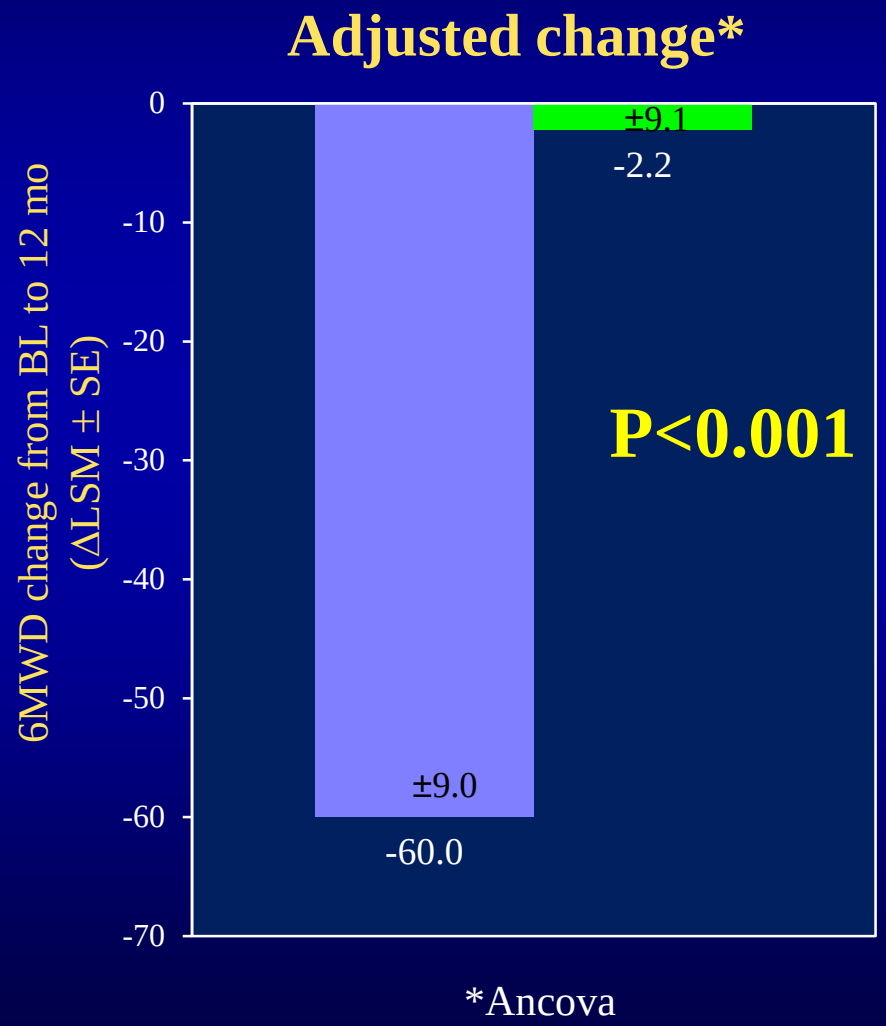
Stone G. et al. NEJM 2018

Transcatheter Mitral-Valve Repair in Patients with Heart Failure

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

Change in 6MWD from Baseline to 12 Months





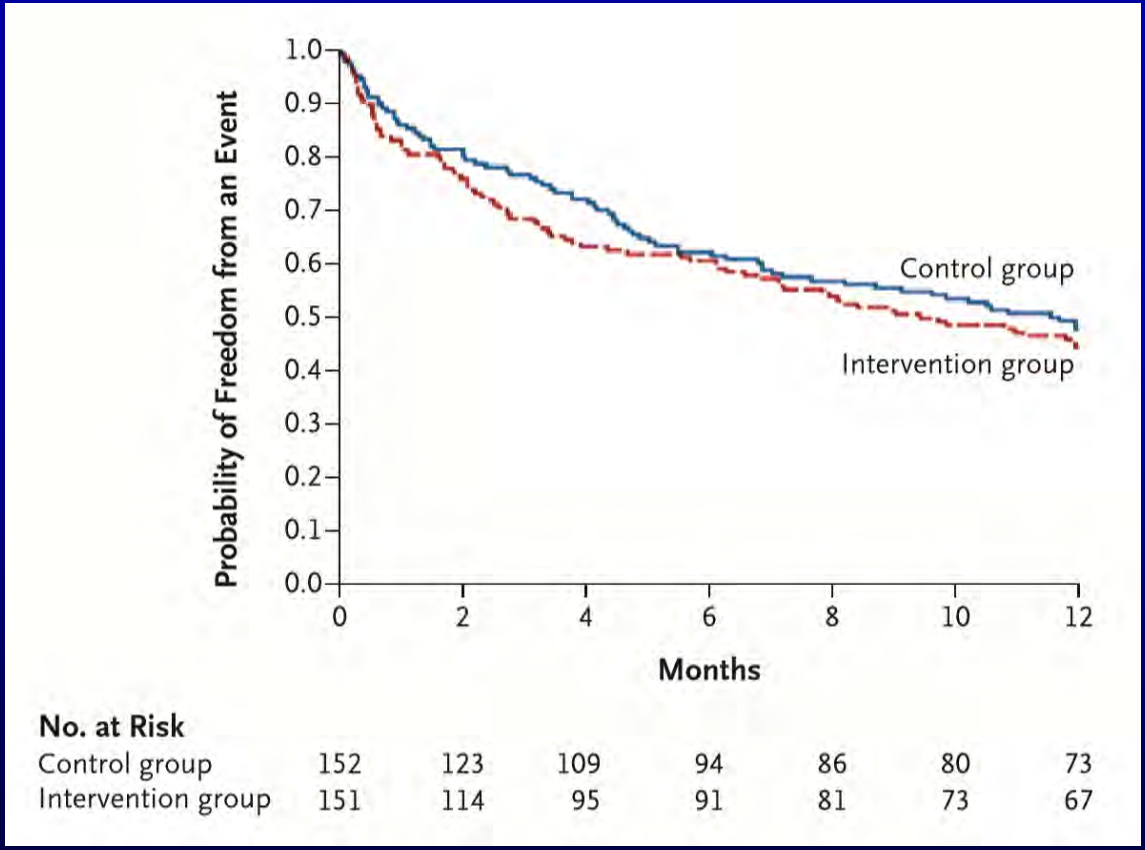
*Ancova

Stone G. et al. NEJM 2018

Percutaneous repair or medical treatment for secondary mitral regurgitation: outcomes at 2 years

MITRA-FR trial: 304 patients with moderate or severe functional MR

- MitraClip: 152
- Medical therapy: 152



No difference in mortality or heart failure hospitalization at 2 years

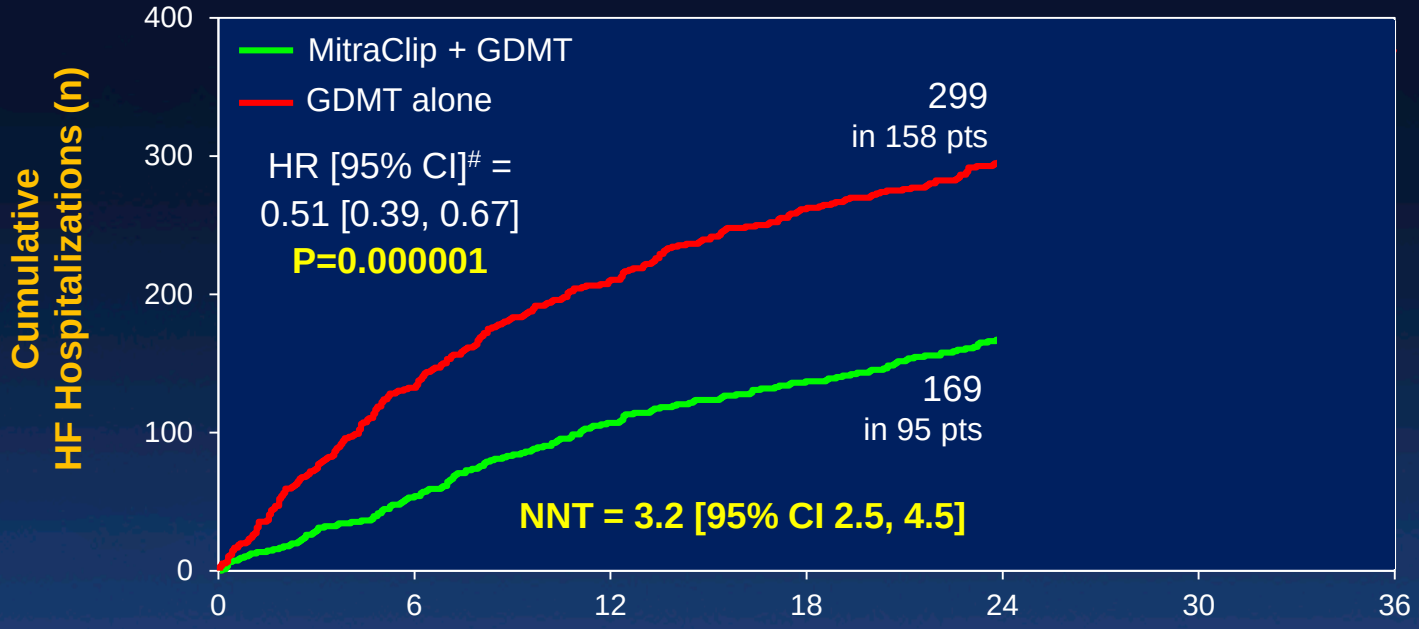
Obadia J-F. et al. NEJM 2018

COAPT TRIAL

Primary Effectiveness Endpoint

All Hospitalizations for HF within 36 months

All patients, ITT, including crossovers



# at Risk:					
MitraClip + GDMT	302	269	238	219	189
GDMT alone	312	272	223	185	144

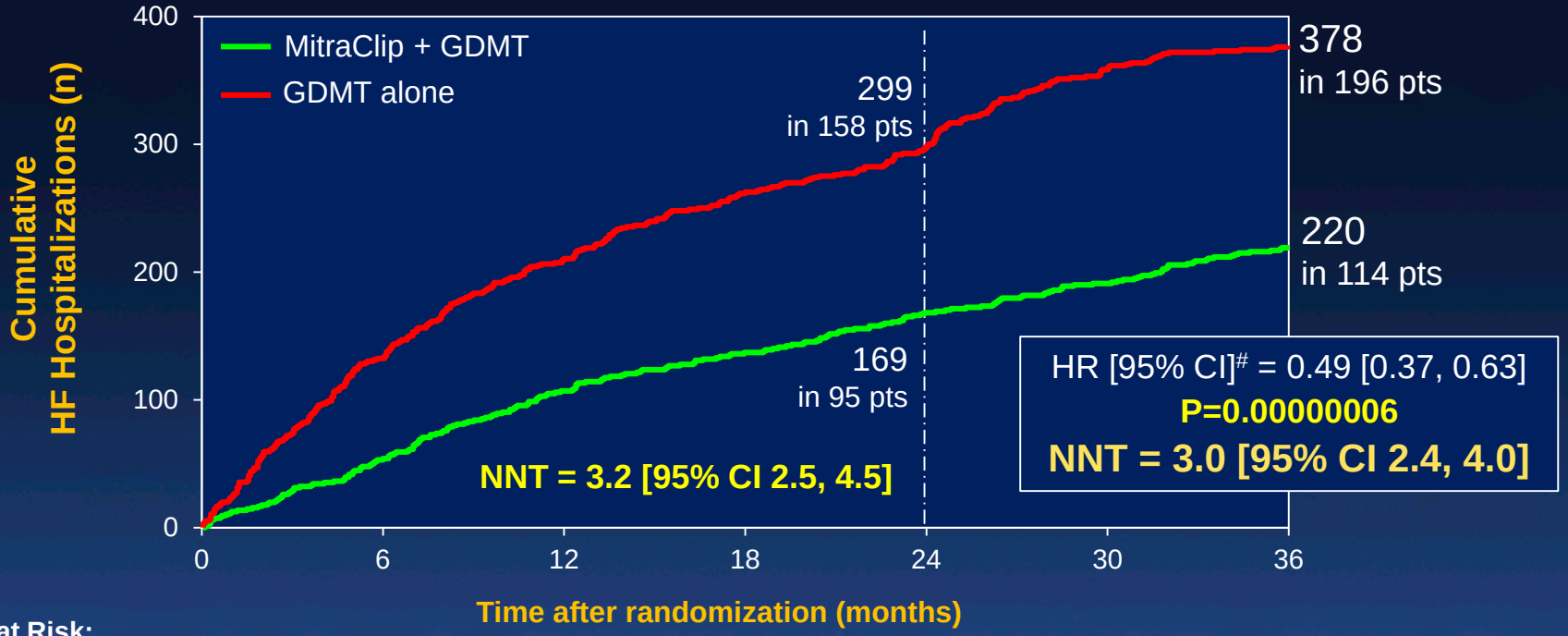
#Joint frailty model

COAPT TRIAL

Primary Effectiveness Endpoint

All Hospitalizations for HF within 36 months

All patients, ITT, including crossovers



# at Risk:							
MitraClip + GDMT	302	269	238	219	189	128	93
GDMT alone	312	272	223	185	144	89	68

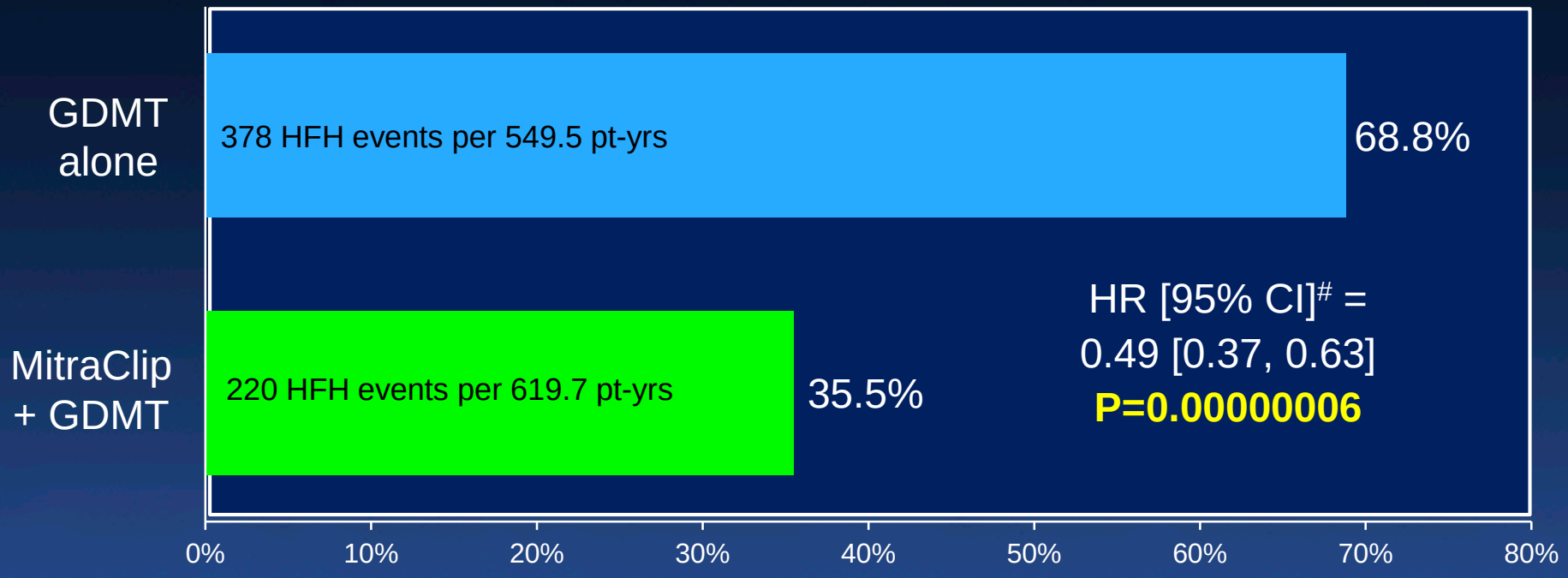
#Joint frailty model

Primary Effectiveness Endpoint

Annualized Rates of HF Hospitalizations within 36 months

All patients, ITT, including crossovers

NNT= 3.0 [95% CI 2.4, 4.0]



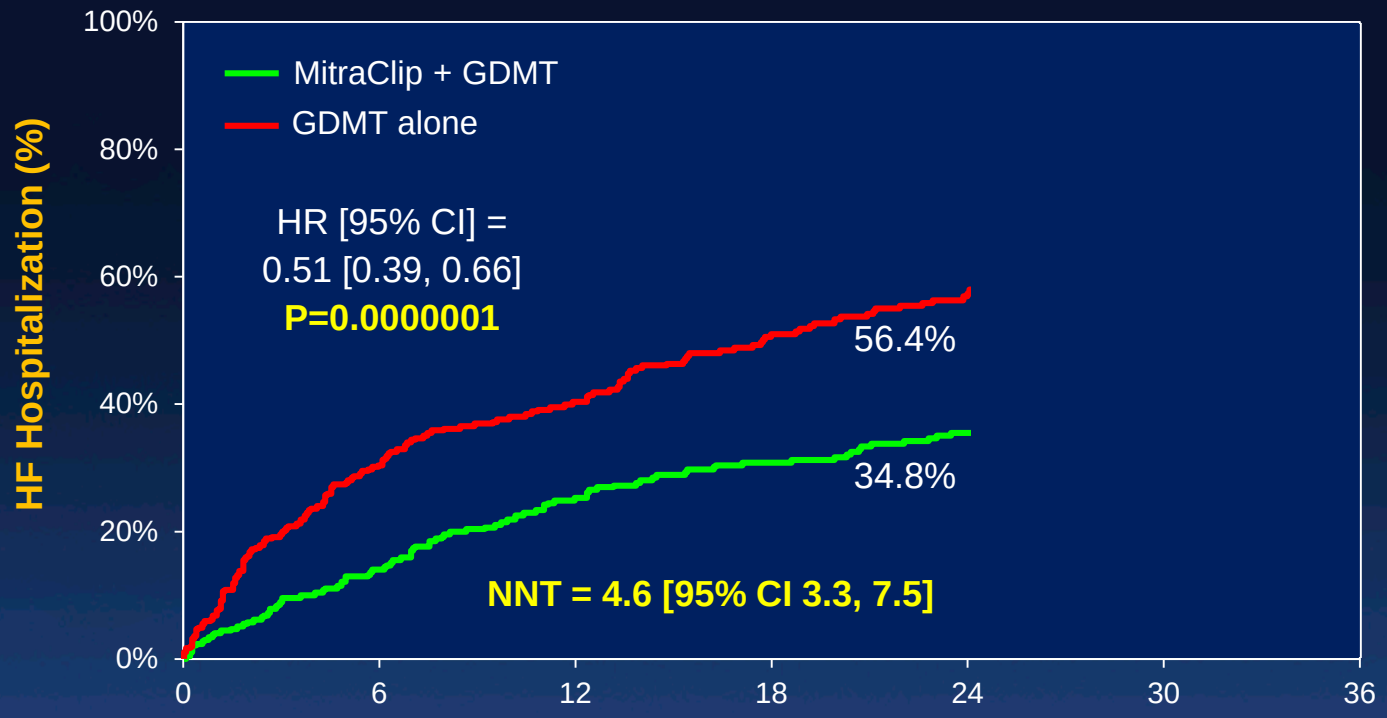
Annualized rate is calculated as total number of HF Hospitalization events divided by total follow-up years

#Joint frailty model

COAPT TRIAL

First Heart Failure Hospitalization

All patients, ITT, including crossovers



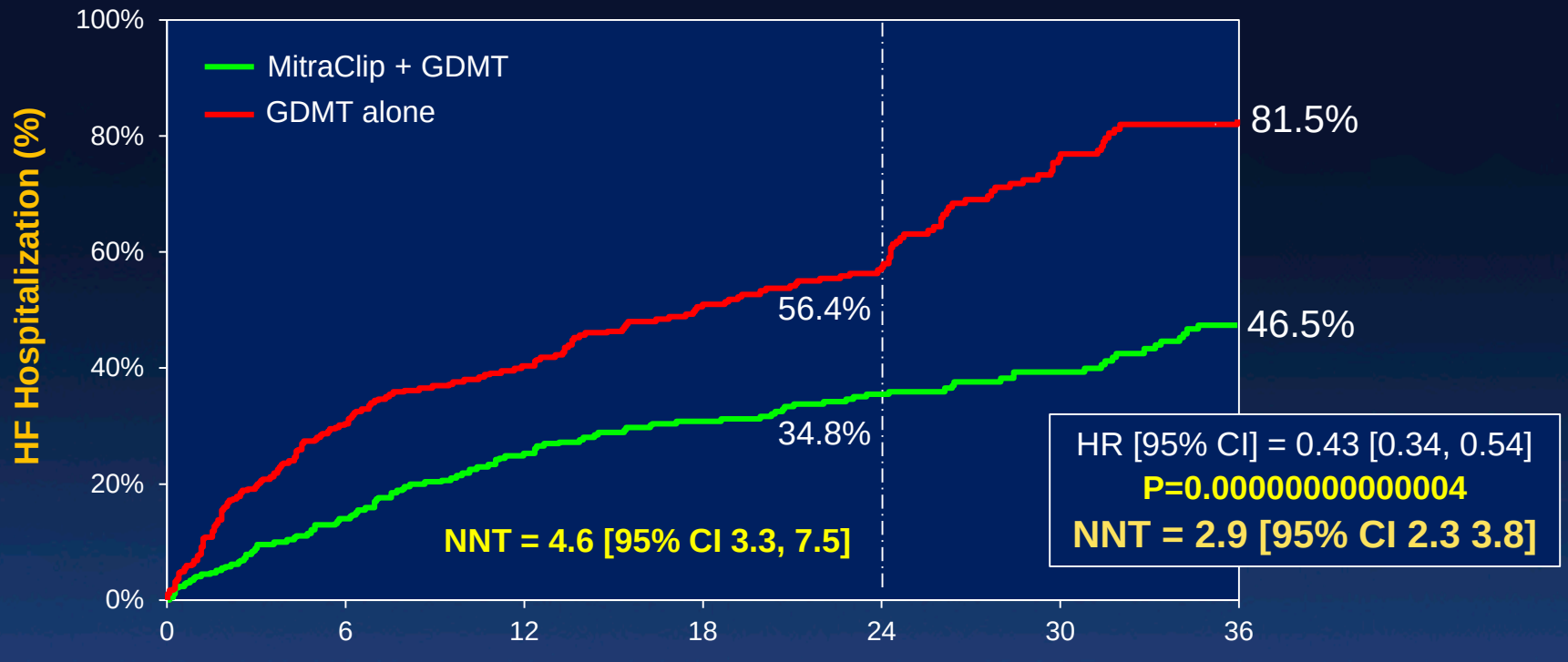
# at Risk:					
MitraClip + GDMT	302	238	196	176	148
GDMT alone	312	206	156	120	87

Event rates are Kaplan-Meier time-to-first event estimates

COAPT TRIAL

First Heart Failure Hospitalization

All patients, ITT, including crossovers



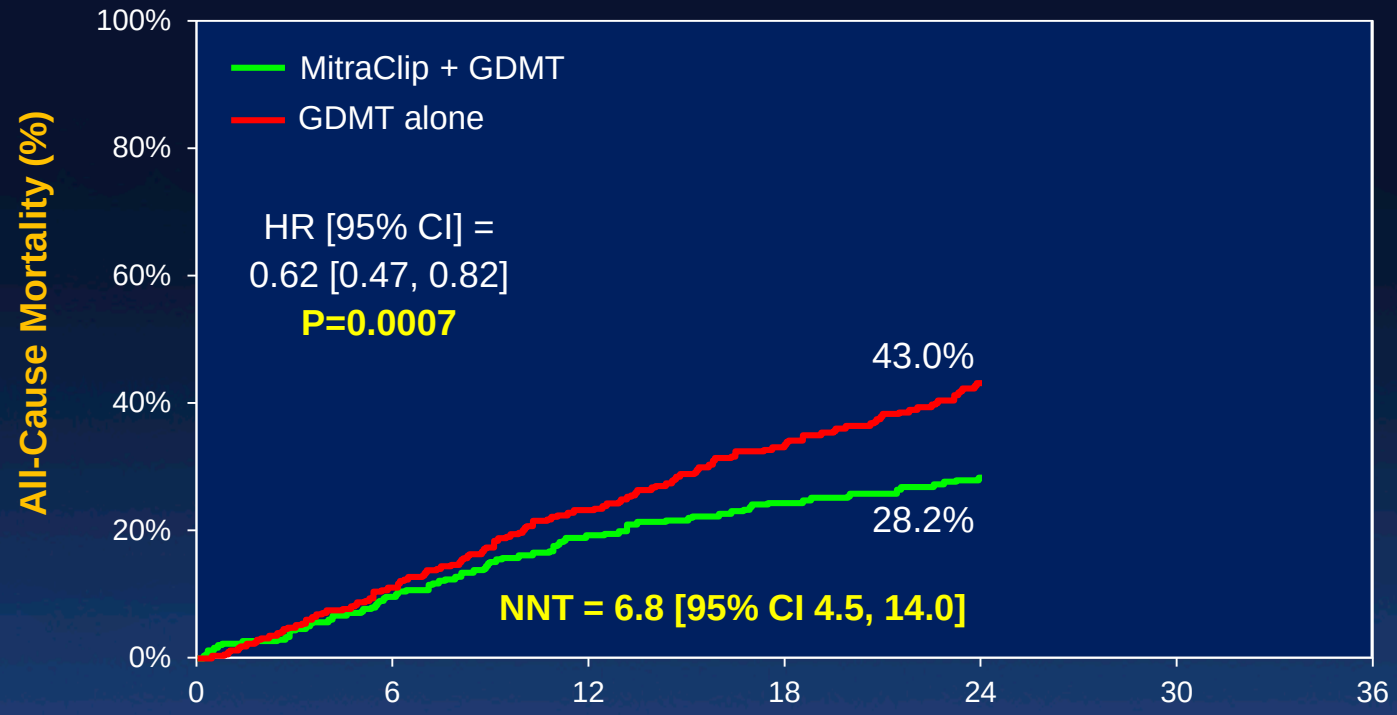
# at Risk:							
MitraClip + GDMT	302	238	196	176	148	101	66
GDMT alone	312	206	156	120	87	37	20

Event rates are Kaplan-Meier time-to-first event estimates

COAPT TRIAL

All-Cause Mortality

All patients, ITT, including crossovers



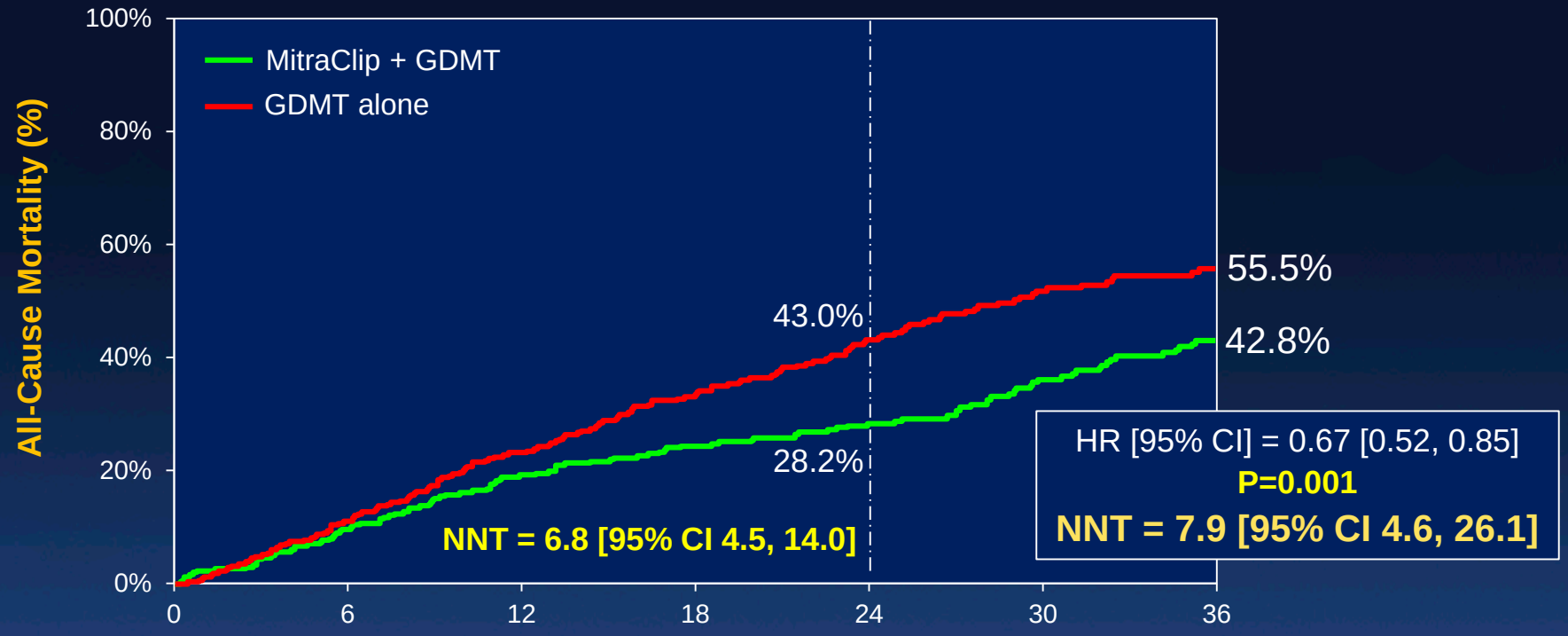
# at Risk:					
MitraClip + GDMT	302	269	238	219	189
GDMT alone	312	272	223	186	145

Event rates are Kaplan-Meier time-to-first event estimates

COAPT TRIAL

All-Cause Mortality

All patients, ITT, including crossovers

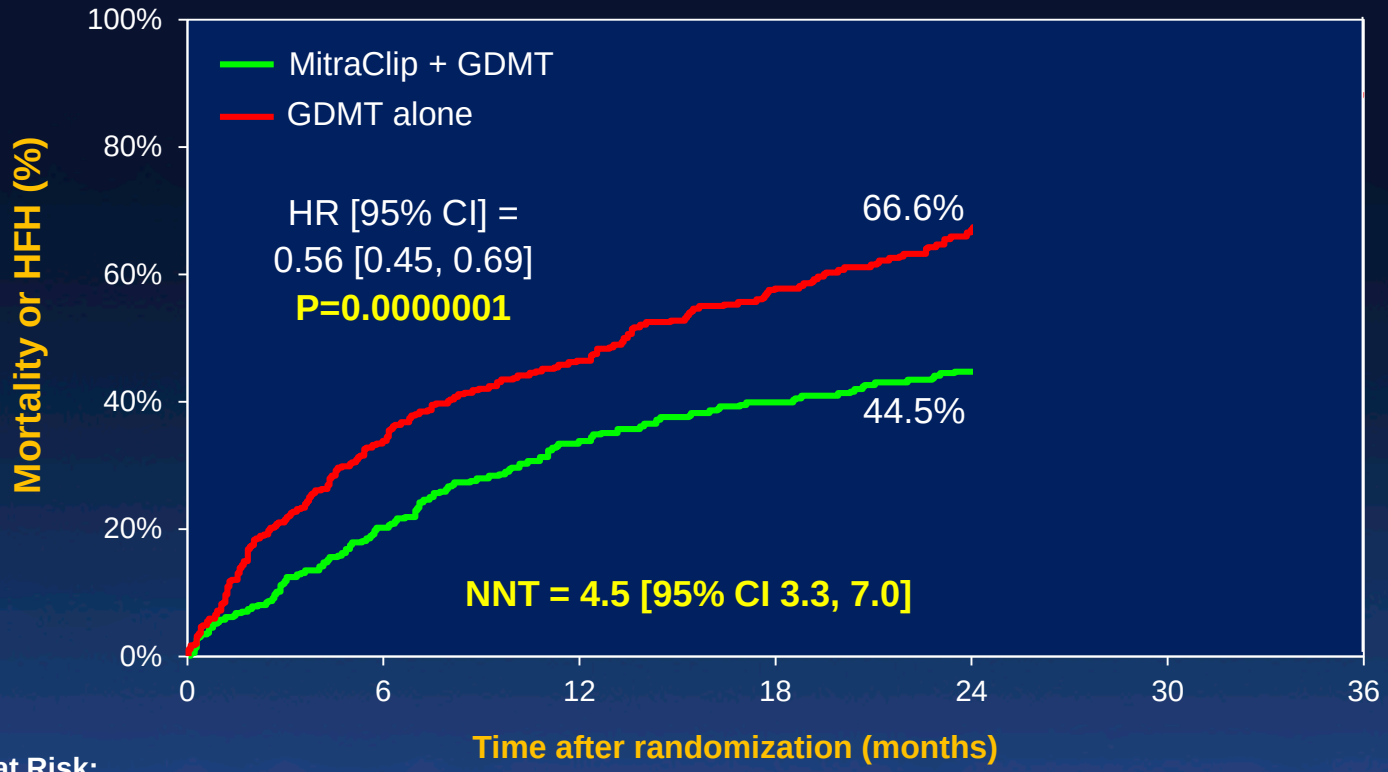


# at Risk:							
MitraClip + GDMT	302	269	238	219	189	128	93
GDMT alone	312	272	223	186	145	91	70

Event rates are Kaplan-Meier time-to-first event estimates

All-Cause Mortality or HF Hospitalization

All patients, ITT, including crossovers

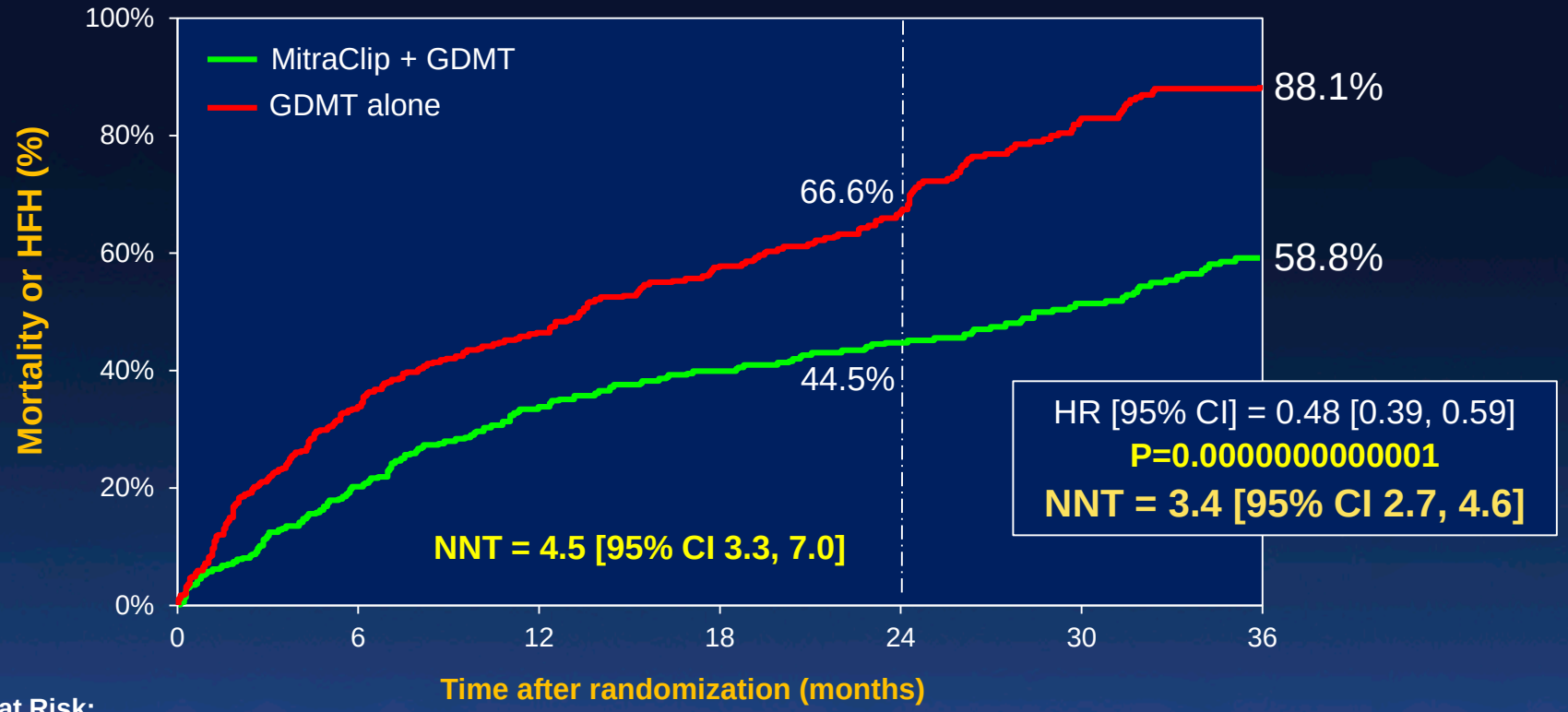


# at Risk:					
MitraClip + GDMT	302	238	196	176	148
GDMT alone	312	206	156	120	87

Event rates are Kaplan-Meier time-to-first event estimates

All-Cause Mortality or HF Hospitalization

All patients, ITT, including crossovers

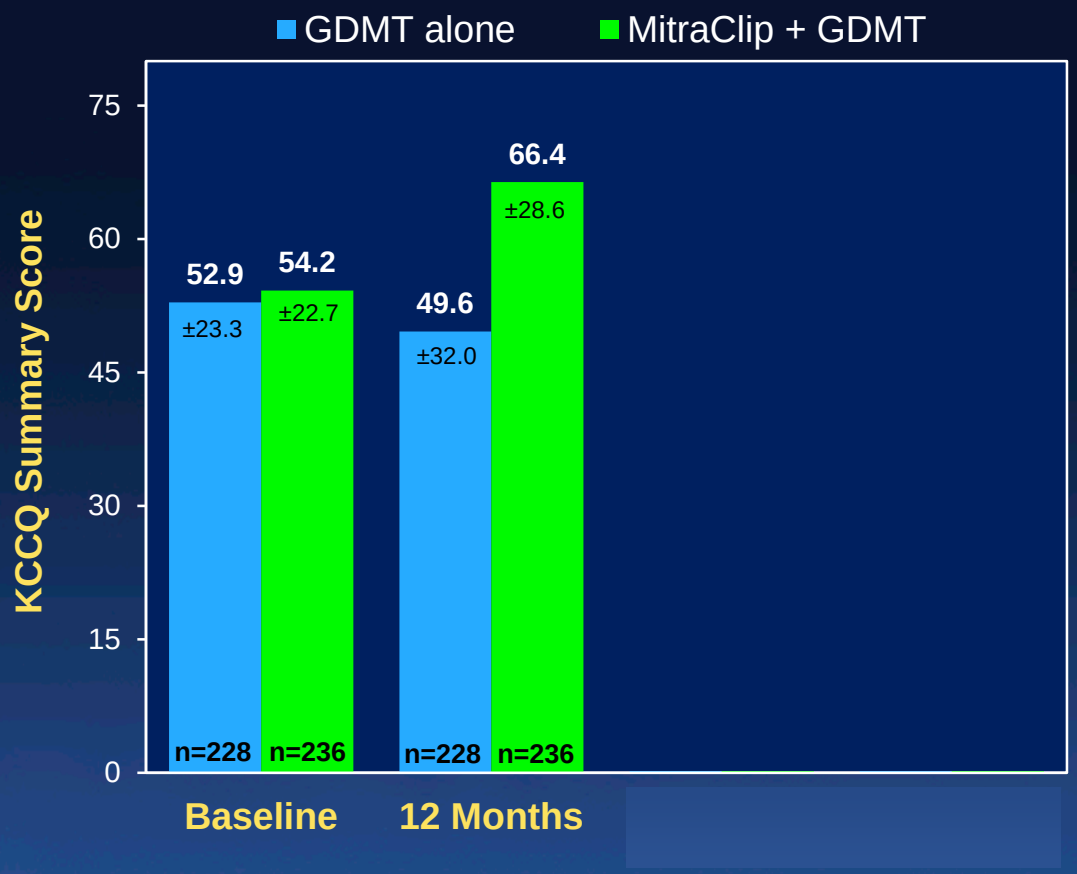


# at Risk:							
MitraClip + GDMT	302	238	196	176	148	101	66
GDMT alone	312	206	156	120	87	37	20

Event rates are Kaplan-Meier time-to-first event estimates

KCCQ Summary Score

All patients, ITT, 24 months

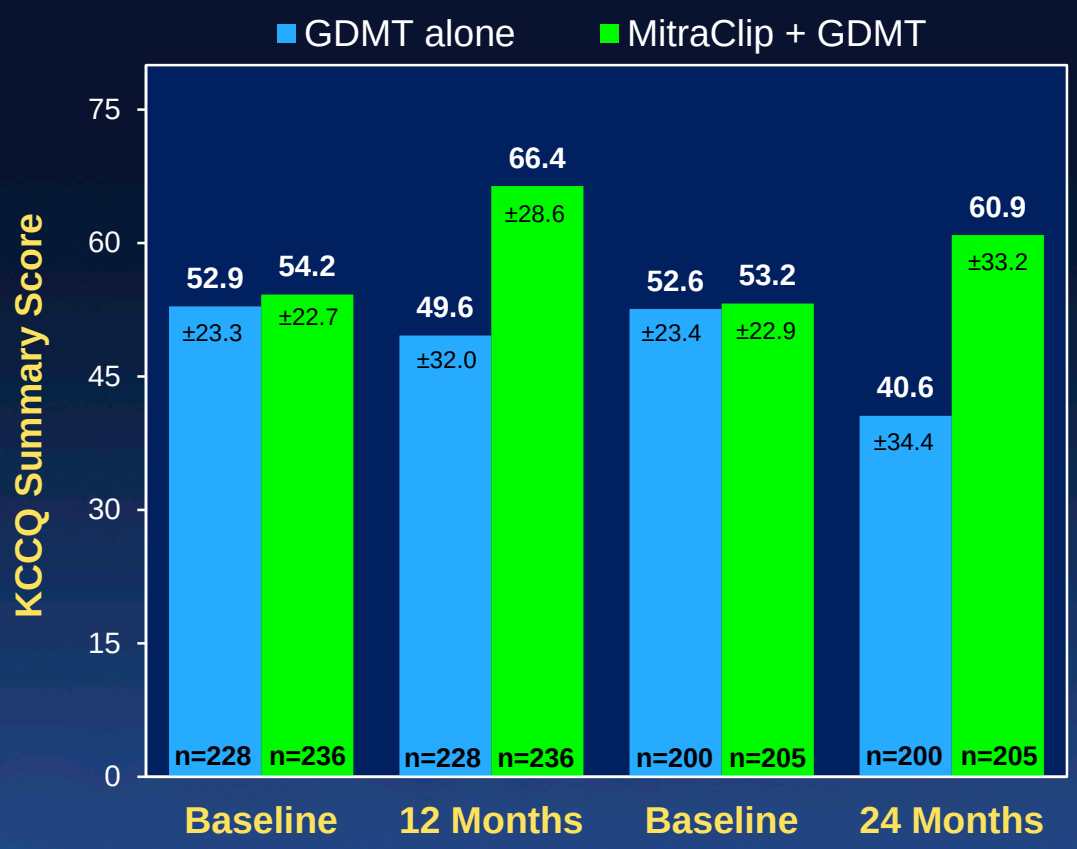


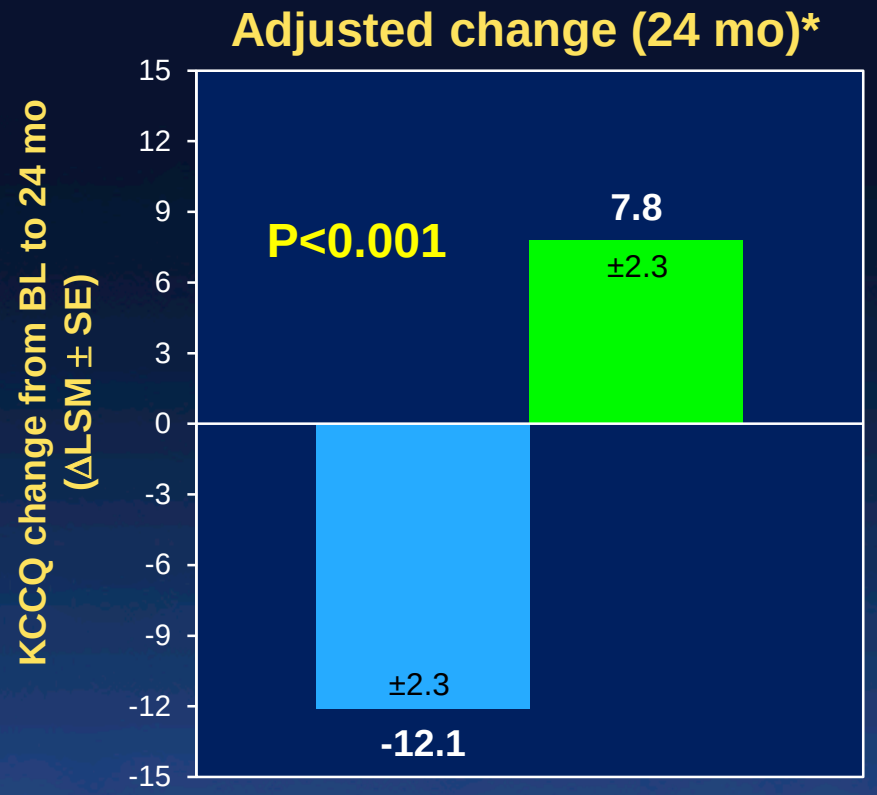
Pts with adjudicated HF death are assigned KCCQ score of 0 at 24 months.
*ANCOVA model with baseline KCCQ and treatment effect as covariates

COAPT TRIAL

KCCQ Summary Score

All patients, ITT, 24 months



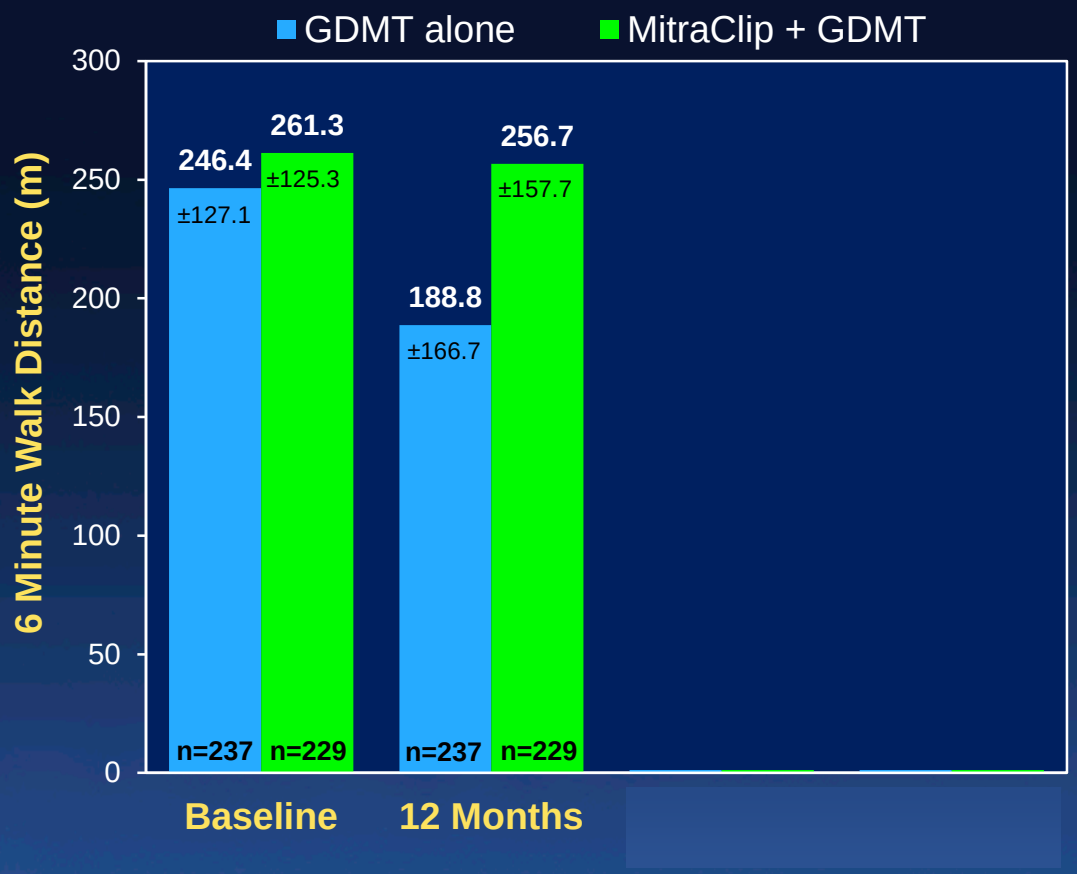


Pts with adjudicated HF death are assigned KCCQ score of 0 at 24 months.
*ANCOVA model with baseline KCCQ and treatment effect as covariates

COAPT TRIAL

6MWD Outcomes

All patients, ITT, 24 months

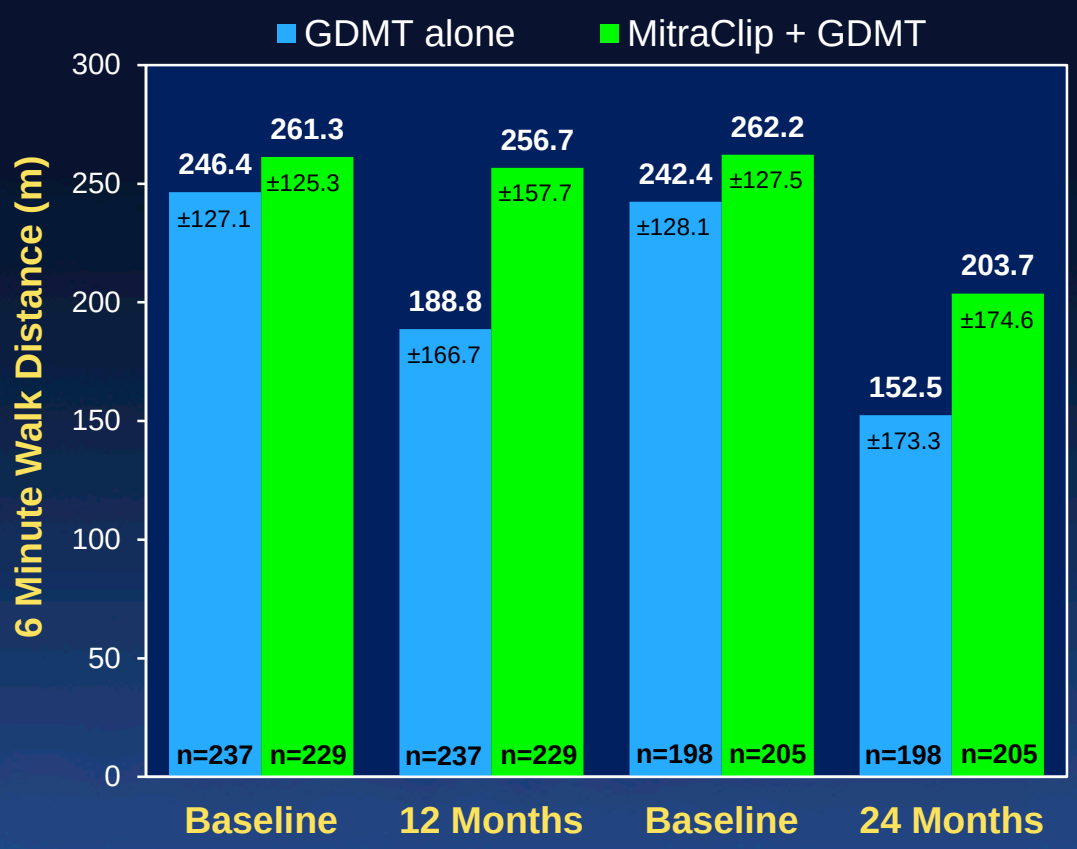


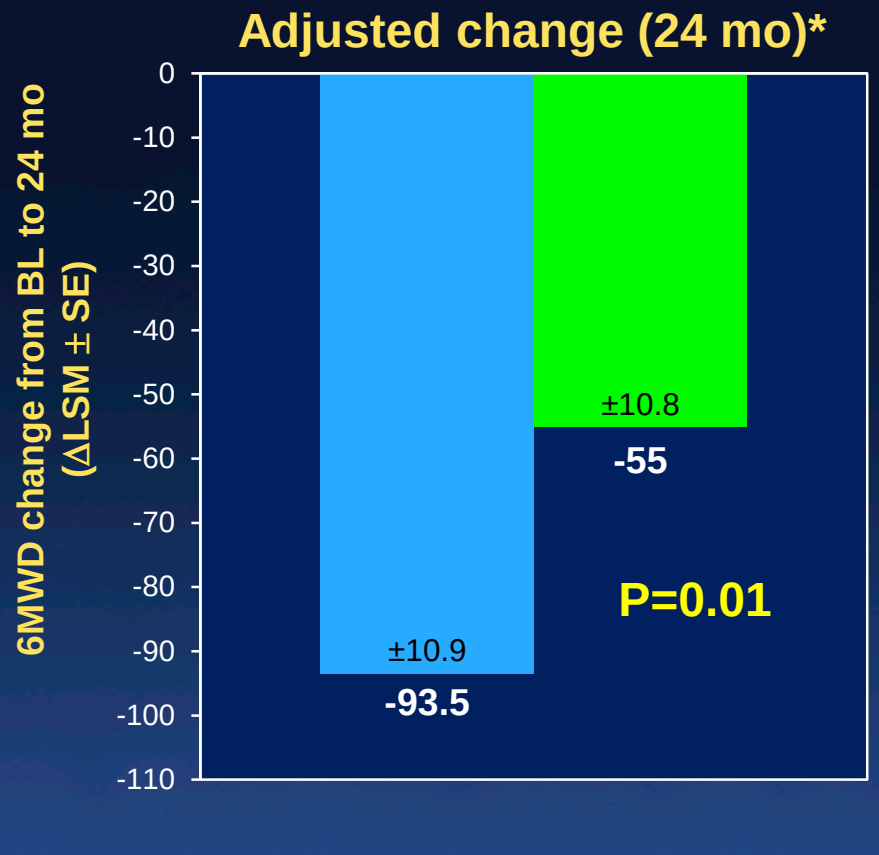
Pts with adjudicated HF death or unable to walk due to cardiac reasons are assigned 6MWD of 0 at 24 months. *ANCOVA model with baseline 6MWD and treatment effect as covariates

COAPT TRIAL

6MWD Outcomes

All patients, ITT, 24 months



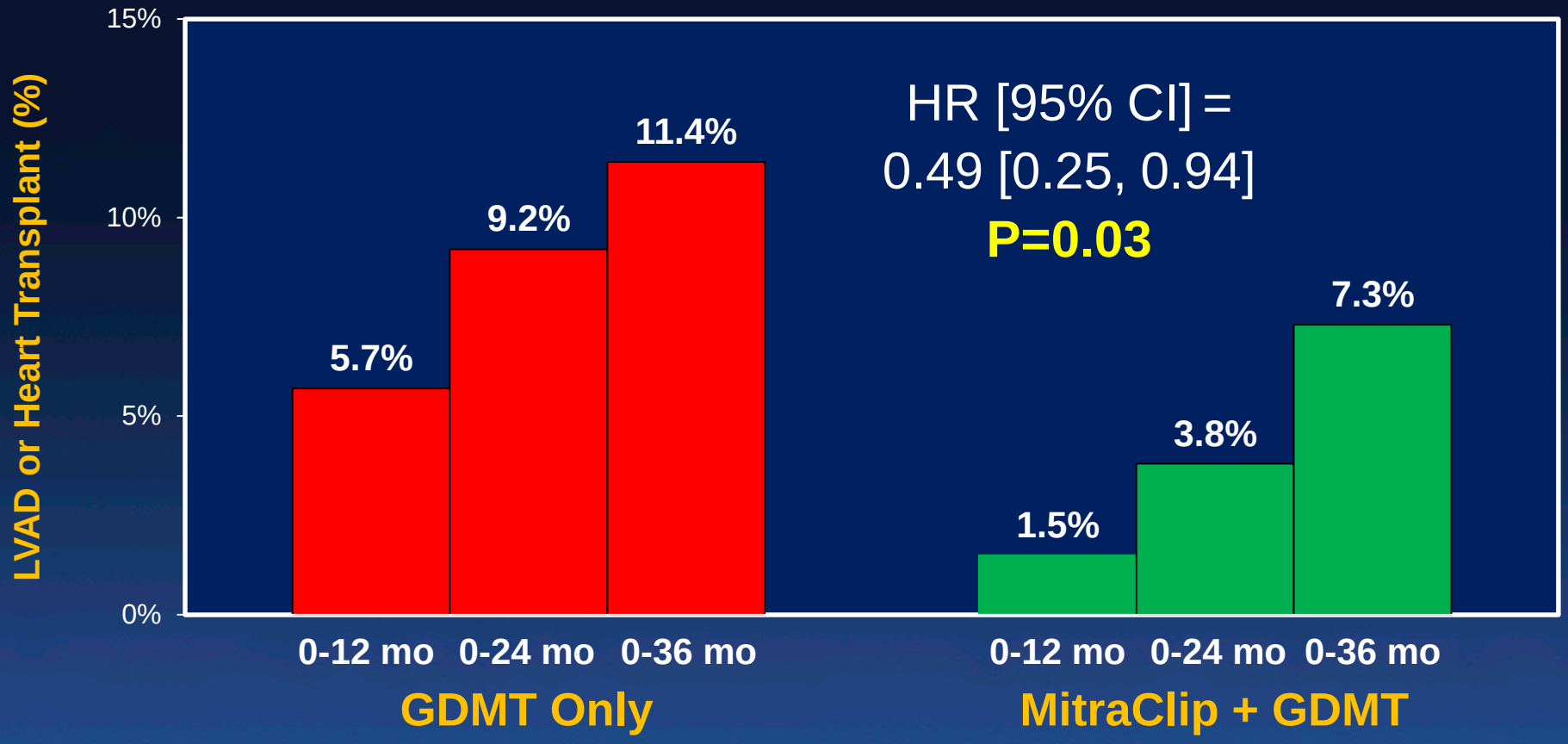


Pts with adjudicated HF death or unable to walk due to cardiac reasons are assigned 6MWD of 0 at 24 months. *ANCOVA model with baseline 6MWD and treatment effect as covariates

COAPT TRIAL

LVAD or Heart Transplantation

All patients, ITT, including crossovers

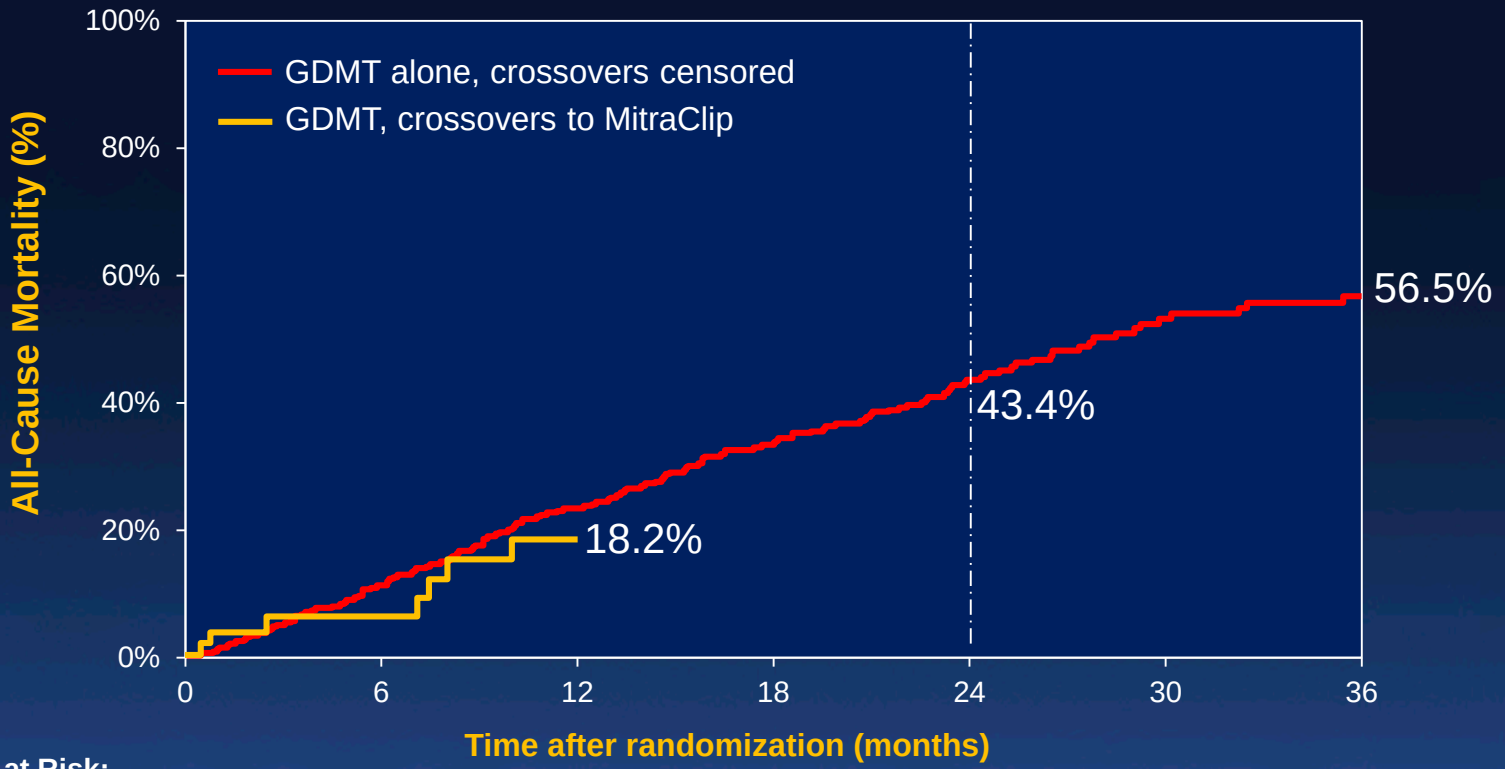


Event rates are Kaplan-Meier time-to-first event estimates

COAPT TRIAL

All-Cause Mortality

GDMT pts censored at time of crossover; Crossovers landmarked at MitraClip procedure



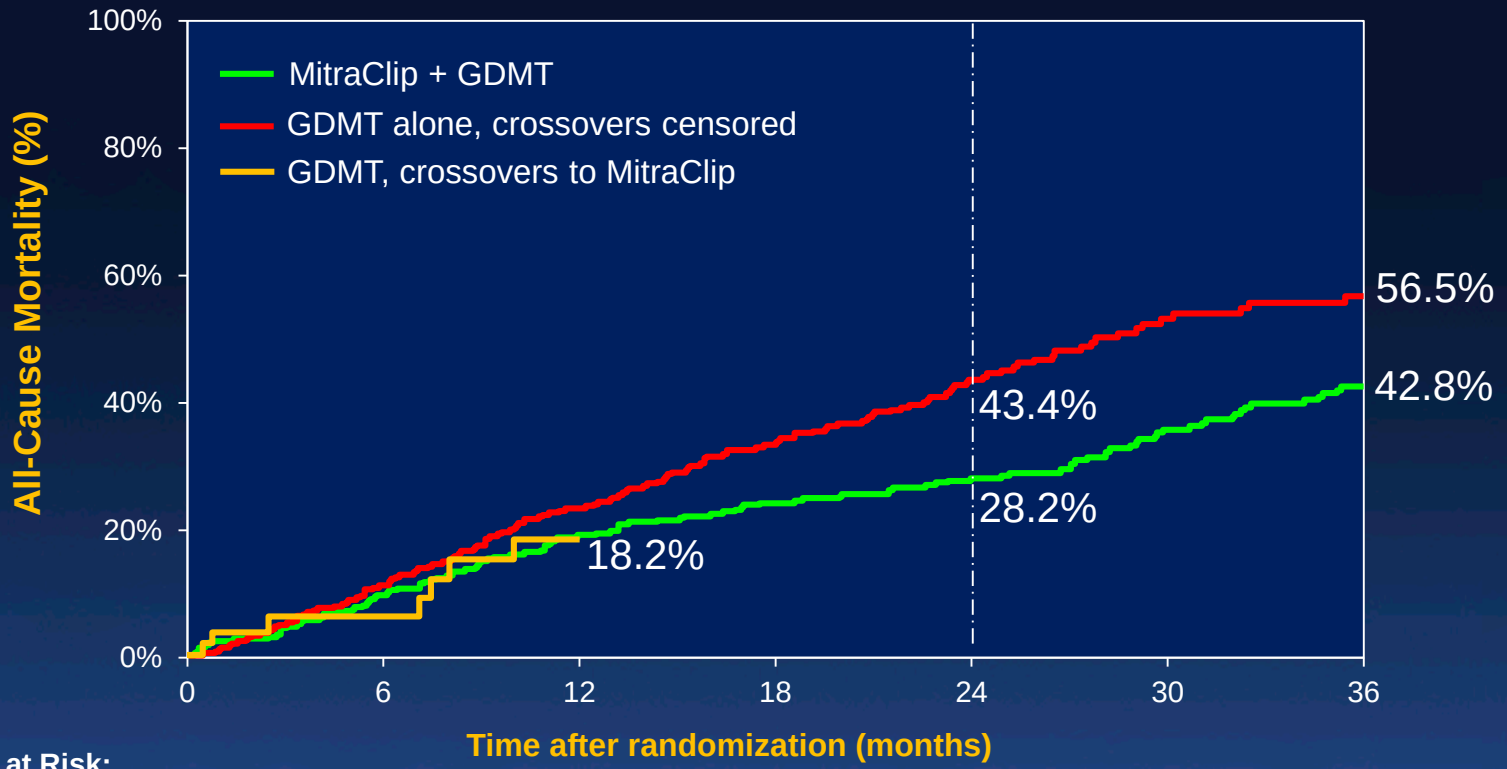
# at Risk:							
GDMT only, crossovers censored	312	271	222	183	134	60	41
GDMT crossovers to MitraClip	58	33	24				

For crossover patients, follow-up duration is from the crossover procedure date; events at procedure dates are excluded. Event rates are Kaplan-Meier time-to-first event estimates, with landmark analysis for crossover patients

COAPT TRIAL

All-Cause Mortality

GDMT pts censored at time of crossover; Crossovers landmarked at MitraClip procedure



# at Risk:							
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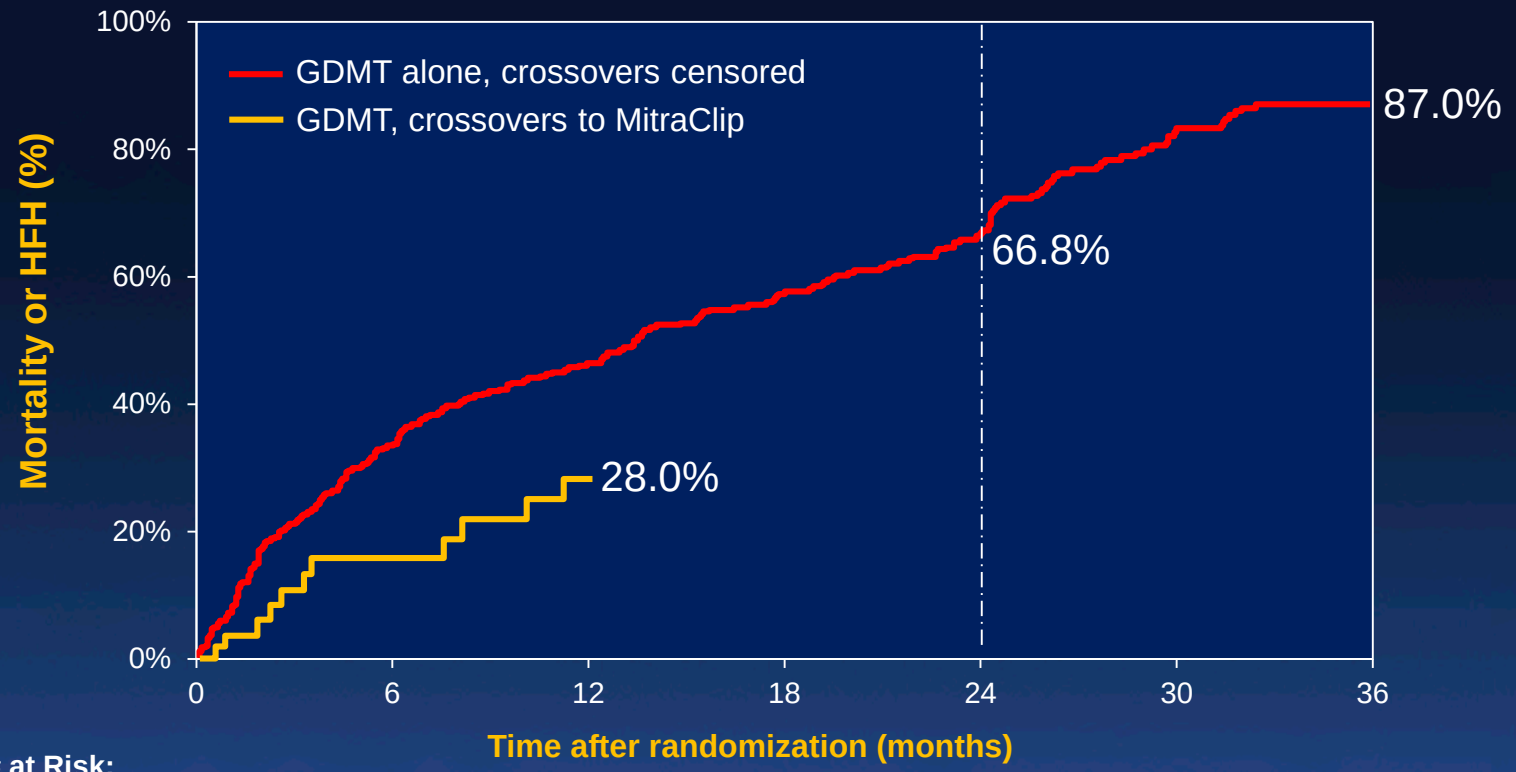
GDMT only, crossovers censored	312	271	222	183	134	60	41
GDMT crossovers to MitraClip	58	33	24				

For crossover patients, follow-up duration is from the crossover procedure date; events at procedure dates are excluded. Event rates are Kaplan-Meier time-to-first event estimates, with landmark analysis for crossover patients

COAPT TRIAL

All-Cause Mortality or HF Hospitalization

GDMT pts censored at time of crossover; Crossovers landmarked at MitraClip procedure



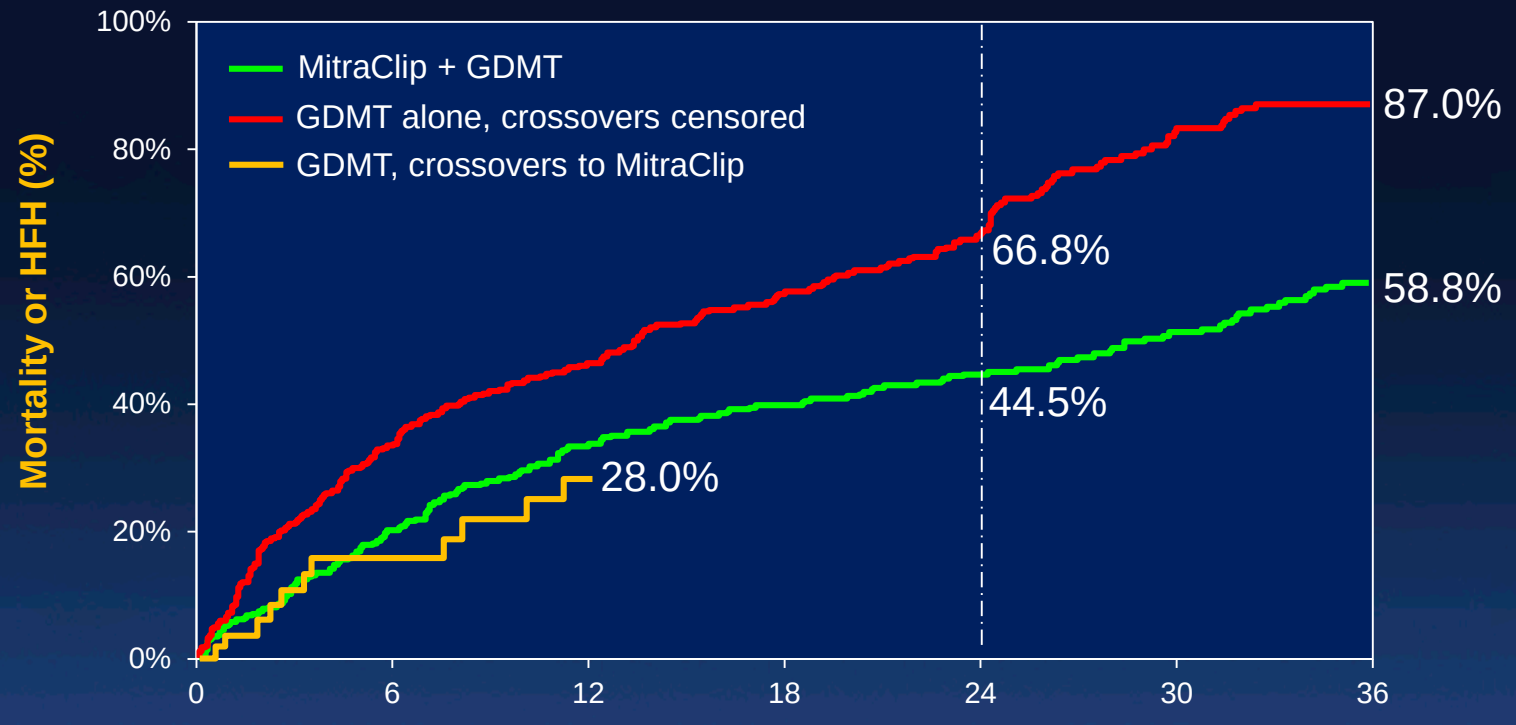
# at Risk:							
GDMT only, crossovers censored	312	205	155	119	85	33	19
GDMT crossovers to MitraClip	58	30	22				

For crossover patients, follow-up duration is from the crossover procedure date; events at procedure dates are excluded. Event rates are Kaplan-Meier time-to-first event estimates, with landmark analysis for crossover patients

COAPT TRIAL

All-Cause Mortality or HF Hospitalization

GDMT pts censored at time of crossover; Crossovers landmarked at MitraClip procedure



# at Risk:							
MitraClip + GDMT	302	238	196	176	148	101	66
GDMT only, crossovers censored	312	205	155	119	85	33	19
GDMT crossovers to MitraClip	58	30	22				

For crossover patients, follow-up duration is from the crossover procedure date; events at procedure dates are excluded. Event rates are Kaplan-Meier time-to-first event estimates, with landmark analysis for crossover patients

MITRA-FR versus COAPT: Lessons from 2 trials with diametrically opposed results

	MITRA-FR	COAPT
Baseline clinical characteristics		
Age, year	70 ± 10	72 ± 11
NYHA class, %		
I	0	0.2
II	32.9	39.0
III	58.5	52.5
IV	8.6	8.3
Surgical risk		
STS score ≥8%		42.7%
EuroSCORE II, median and IQR	6.2 (3.5–11.0)	
Baseline echocardiographic characteristics		
MR severity, %		
Moderate (EROA 20-29 mm^2)	52	14
Moderate-to-severe (EROA 30-39 mm^2)	32	46
Severe (EROA ≥ 40 mm^2)	16	41
EROA, mm^2	31 ± 10	41 ± 15
LV end-diastolic volume index, mL/m^2	135 ± 35	101 ± 34
LV ejection fraction, %	33 ± 7	31 ± 9

- **COAPT: More severe MR compared to the degree of LV dysfunction**
- **MITRA-FR: Less severe MR compared to the degree of LV dysfunction**

Pibarot P. et al. EHJ-Cardiovascular Imaging 2018

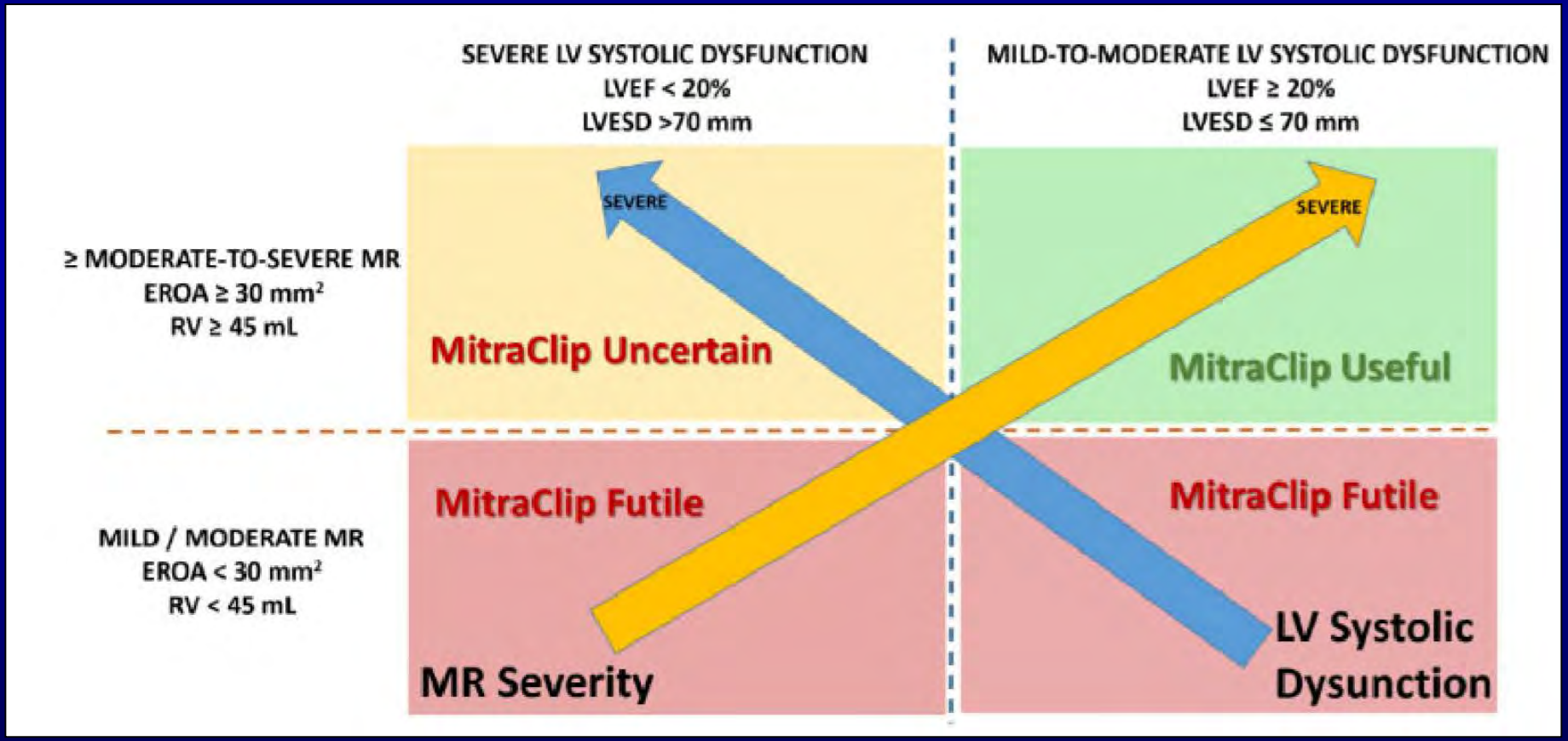
MITRA-FR versus COAPT: Lessons from 2 trials with diametrically opposed results

- **COAPT**: Greater MR reduction with fewer complications
- **MITRA-FR**: Less MR reduction with increased complications

	MITRA-FR	COAPT
Procedural characteristics and outcomes[a]		
Procedural success, %[a]	96	98
Procedural complications, %[a]	14.6	8.5
Number of clips, %[b]		
1 Clip	46	36
2 Clips	45	55
3 Clips	9	8
4 Clips	0	0.3
Post-procedural MR ≥ moderate-to-severe (3+), %[a]		
End of procedure	9	5
1 year post-procedure	17	5
2 years post-procedure		0.9

Pibarot P. et al. EHJ-Cardiovascular Imaging 2018

MITRA-FR versus COAPT: Lessons from 2 trials with diametrically opposed results

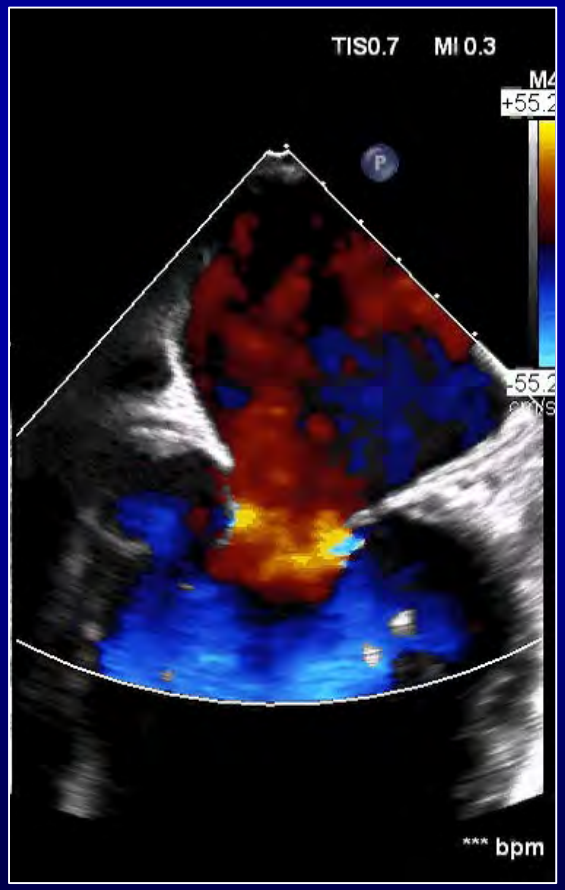


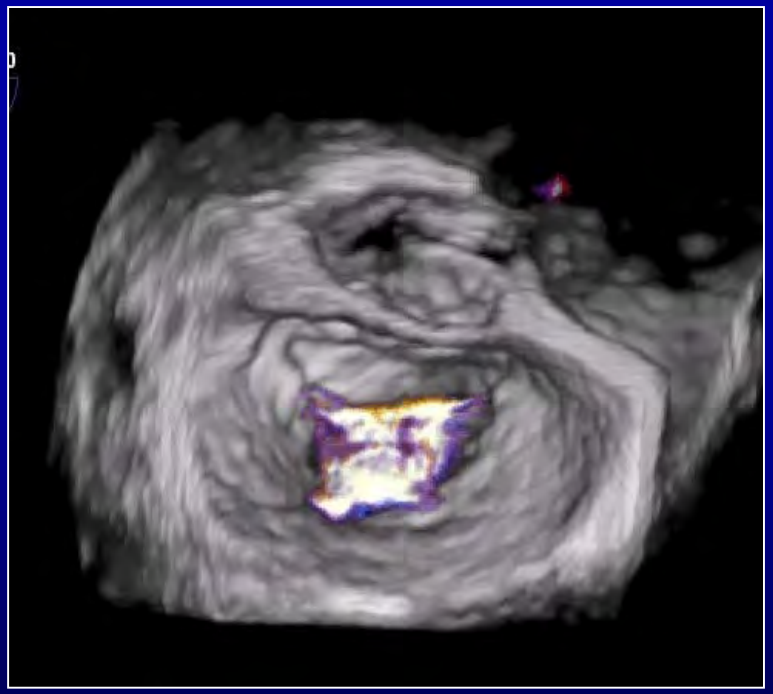
Pibarot P. et al. EHJ-Cardiovascular Imaging 2018

72 y/o male presenting in cardiogenic shock to outside hospital

Patient optimized and transferred to Cedars-Sinai on milrinone drip for MitraClip

Severe functional MR, EF 20%



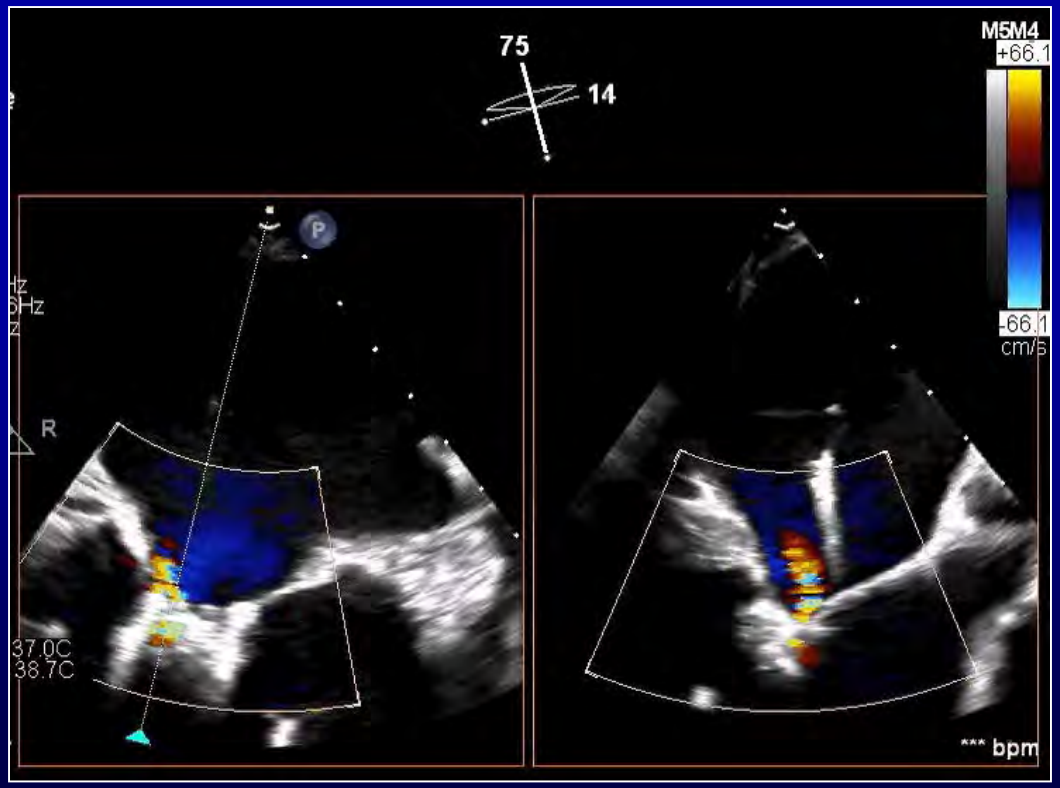


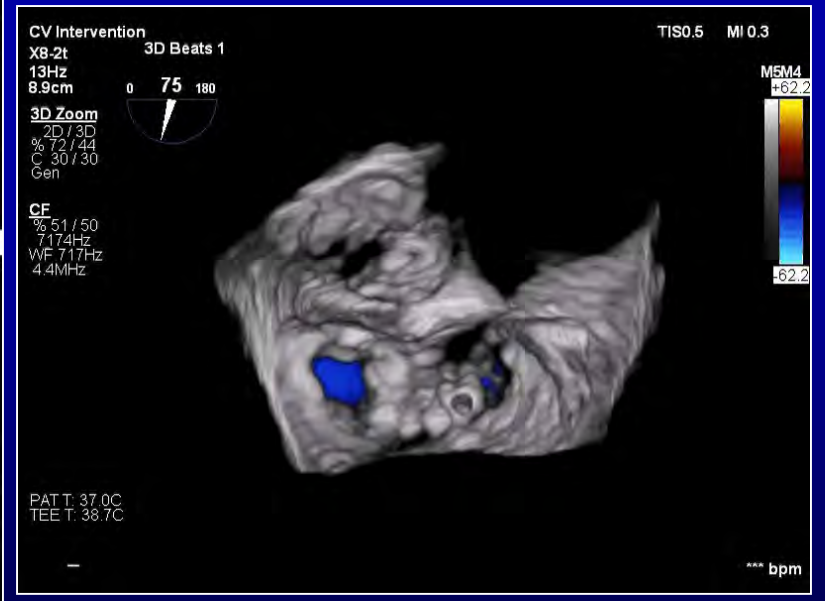
72 y/o male presenting in cardiogenic shock to outside hospital

Patient optimized and transferred to Cedars-Sinai on milrinone drip for MitraClip

s/p MitraClip x 3, patient discharged home on POD#1

NYHA 2





March 14, 2019
FDA approves MitraClip for functional MR

FDA NEWS RELEASE

FDA approves new indication for valve repair device to treat certain heart failure patients with mitral regurgitation

Not all patients with degenerative MR are candidates for percutaneous mitral valve repair

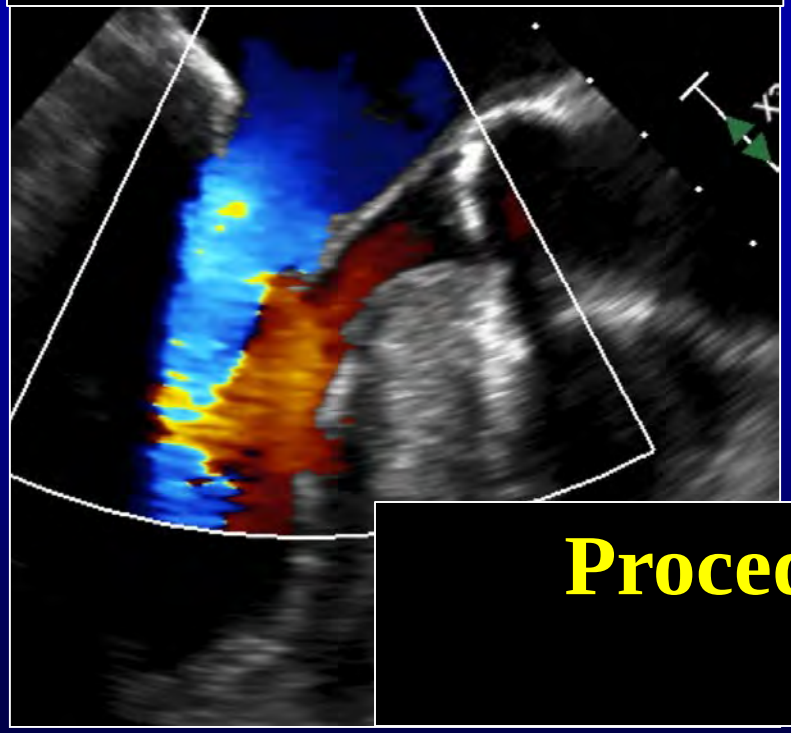
- Low surgical risk and good surgical candidate
- Small valve
- Mitral annular calcification
- Leaflet perforation
- High baseline mitral valve gradients

83 y/o female referred for MitraClip for MR and LVOT obstruction

Known history of HOCM, managed on medications for > 10 years, but now worsening heart failure, MR and LVOT obstruction

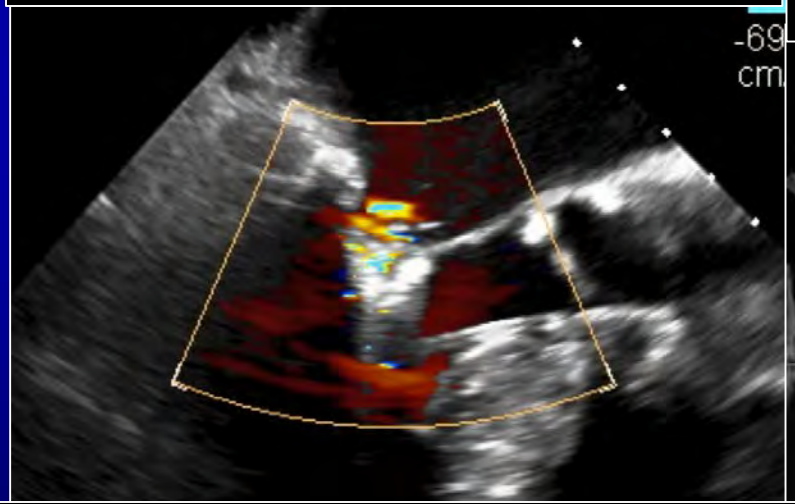
Baseline

SAM, LVOT obstruction and moderate MR

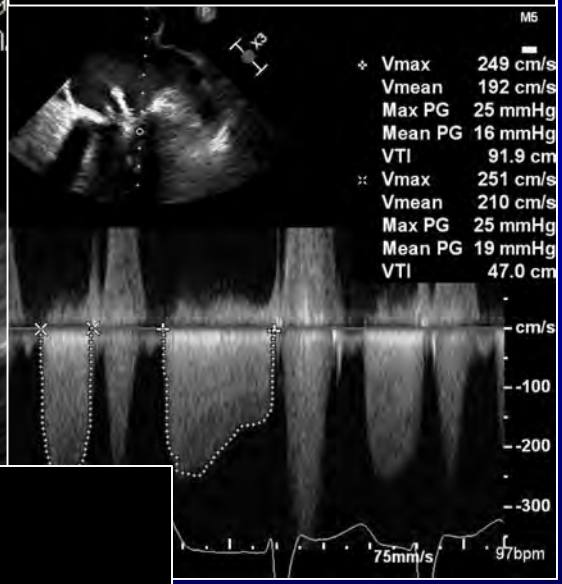


s/p MitraClip x 1

Trivial MR, no LVOT obstruction



Rise in mitral valve gradient to 19mmHg

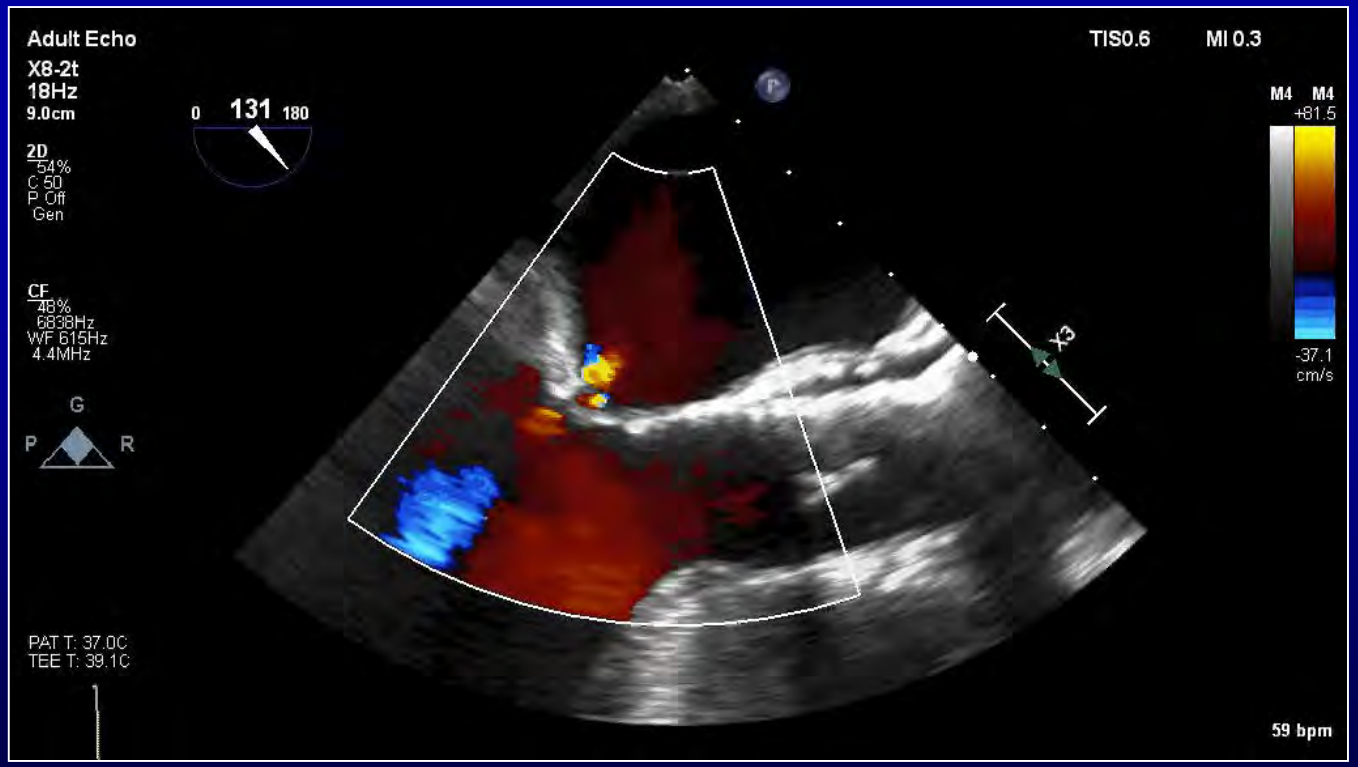


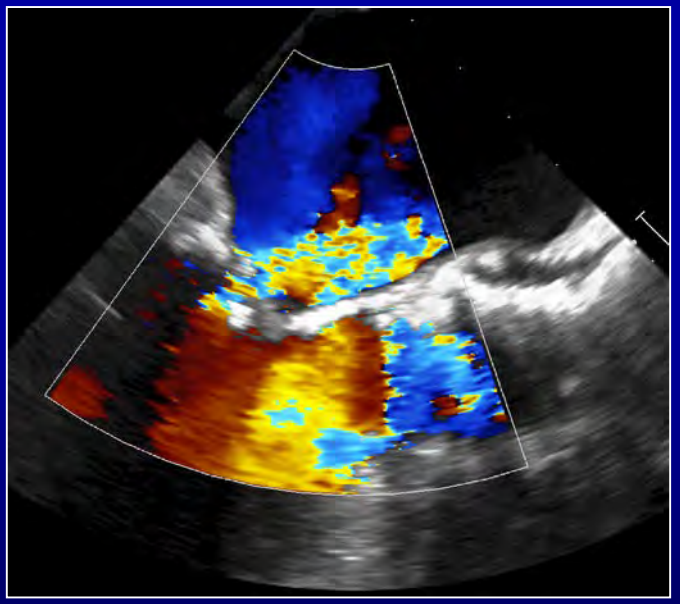
Procedure aborted, clip not deployed

79 y/o female referred for MitraClip

H/o TAVR complicated by infective endocarditis 1 year ago, currently in remission

Leaflet perforation with severe MR on TEE
Likely due to prior infective endocarditis
Patient referred for surgery

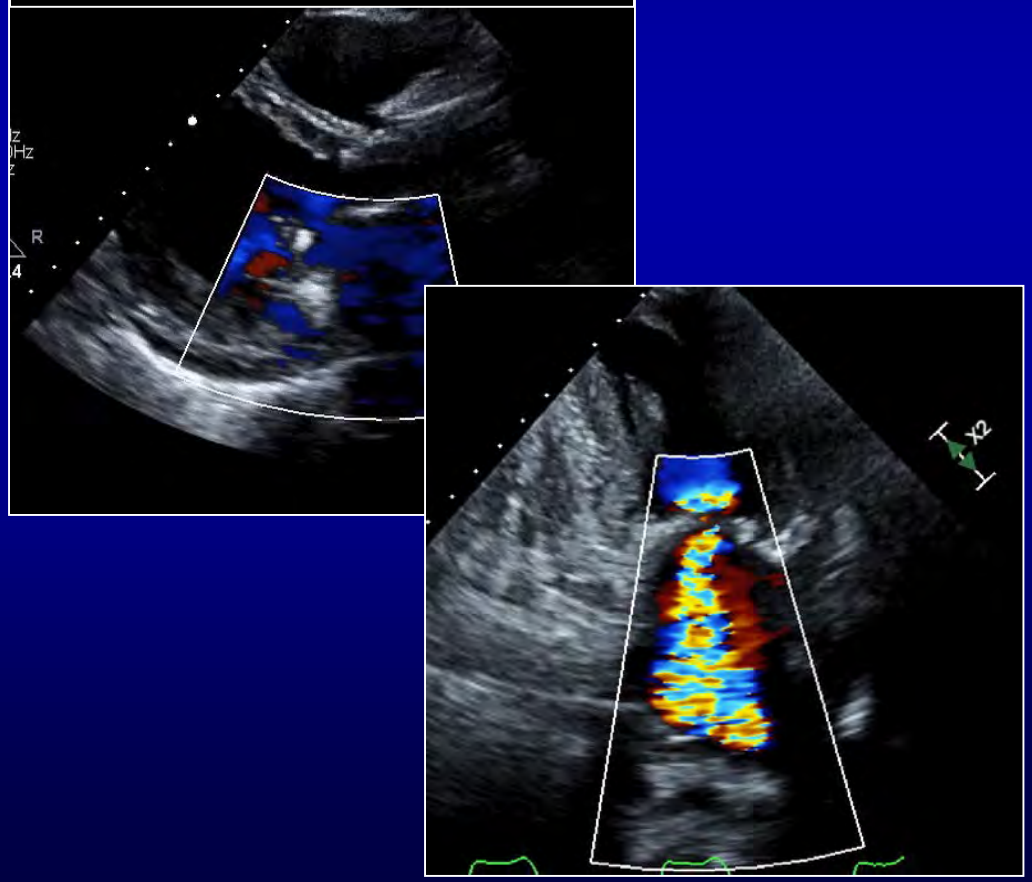




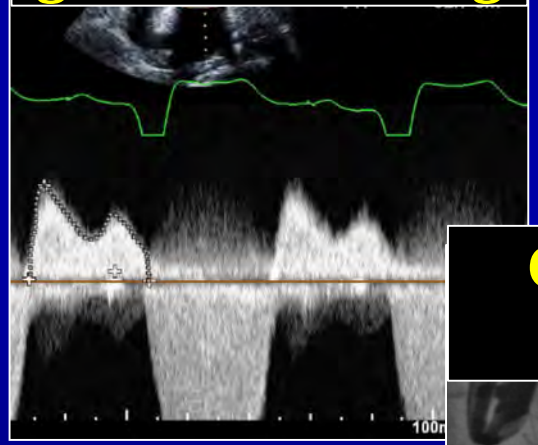
90 y/o female referred for percutaneous mitral valve intervention

Due to severe MAC and high mitral valve gradient, patient turned down for MitraClip and is being evaluated for TMVR.

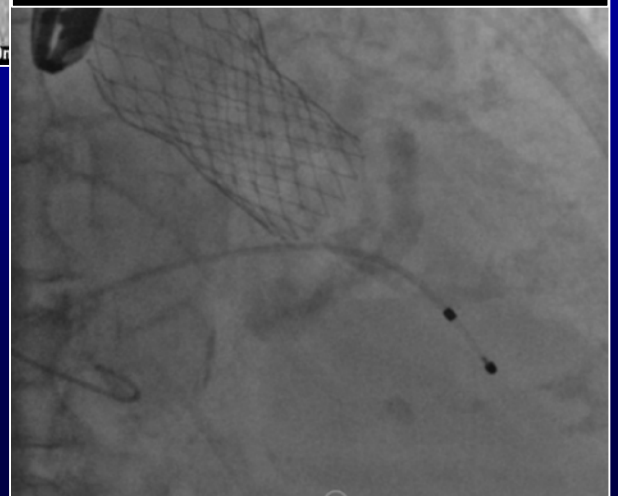
Severe MR



Mean mitral gradient 8mmHg

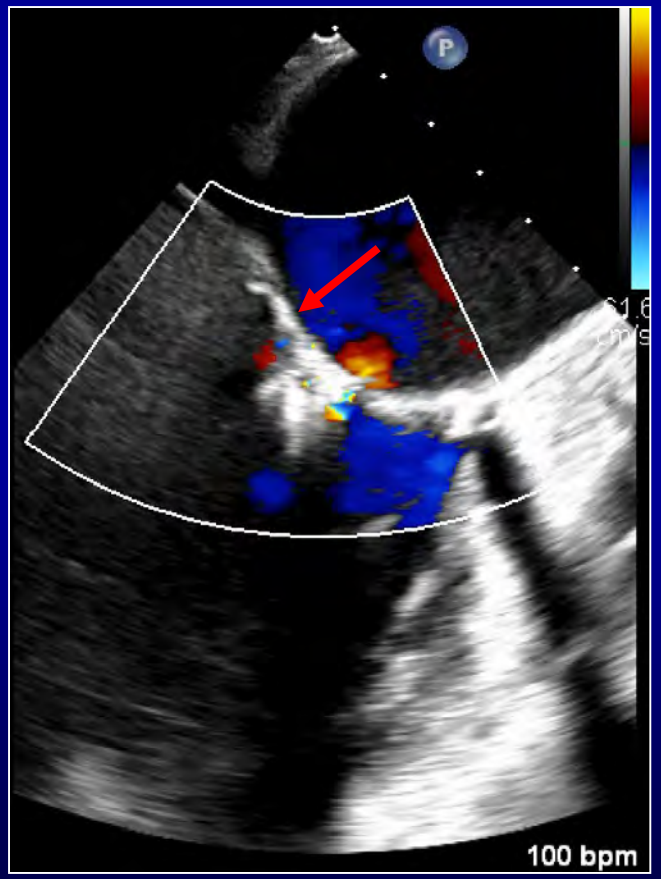


Circumferential MAC

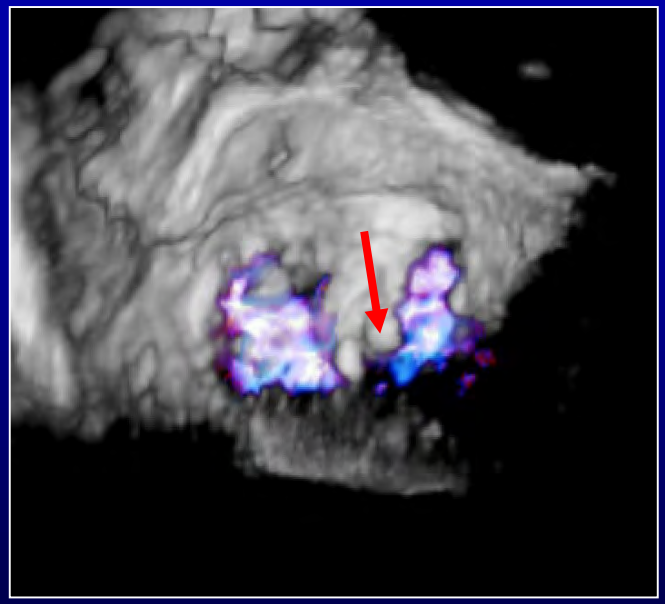


81 y/o female presenting with heart failure

History of MitraClip 2 years ago, now with severe recurrent MR



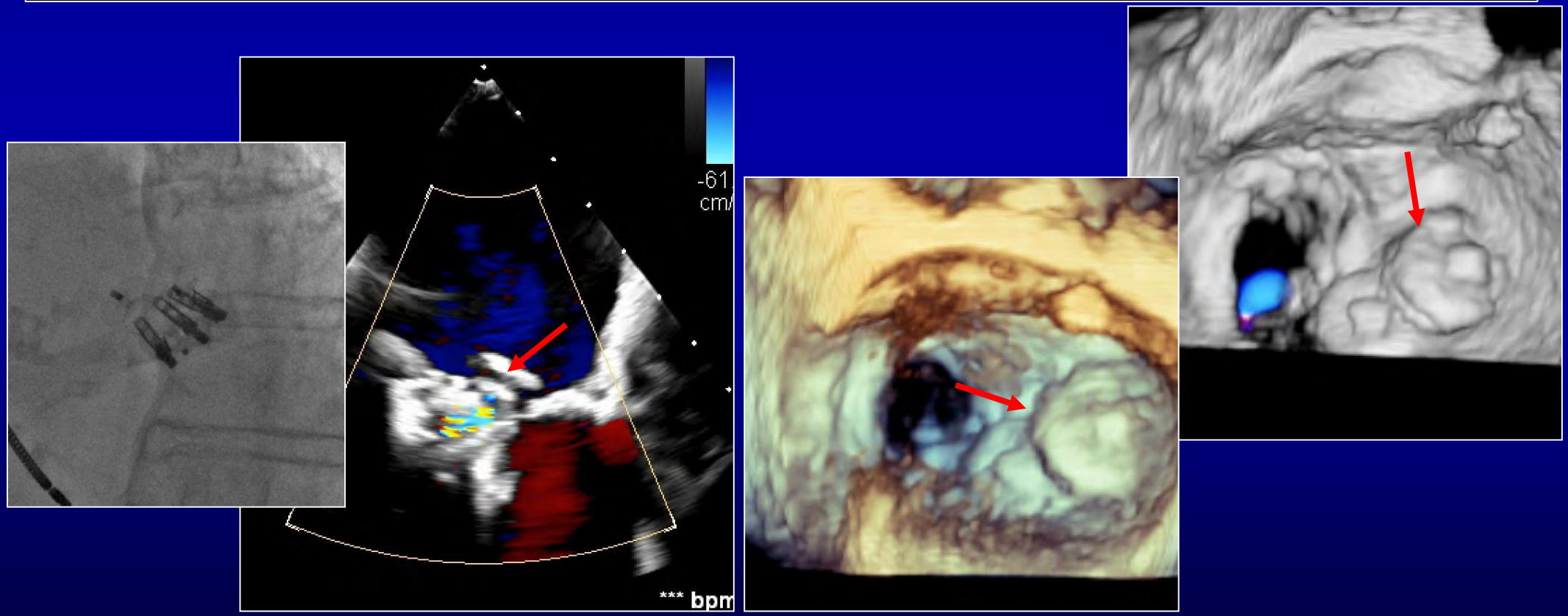
Leaflet perforation due to the previously implanted clip, with severe regurgitation from the perforation



81 y/o female presenting with heart failure

History of MitraClip 2 years ago, now with severe recurrent MR

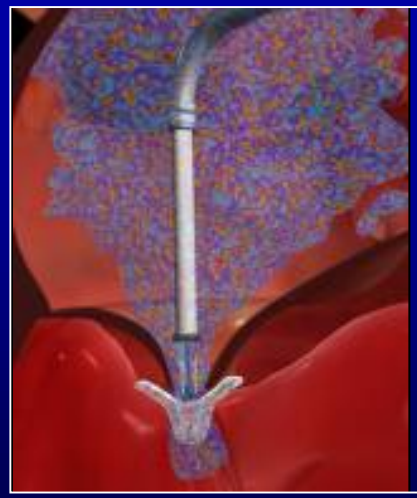
s/p deployment of 1 additional clip followed by plugging of the perforated mitral leaflet with AVP vascular plugs



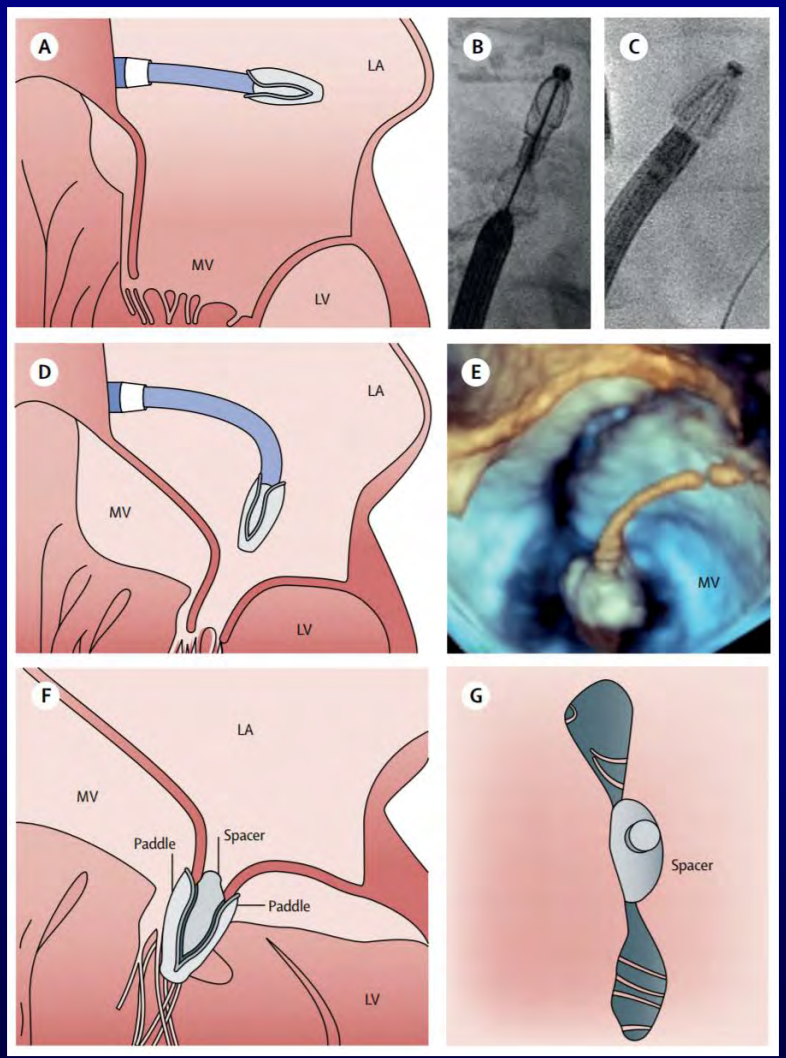
Transcatheter mitral valve repair

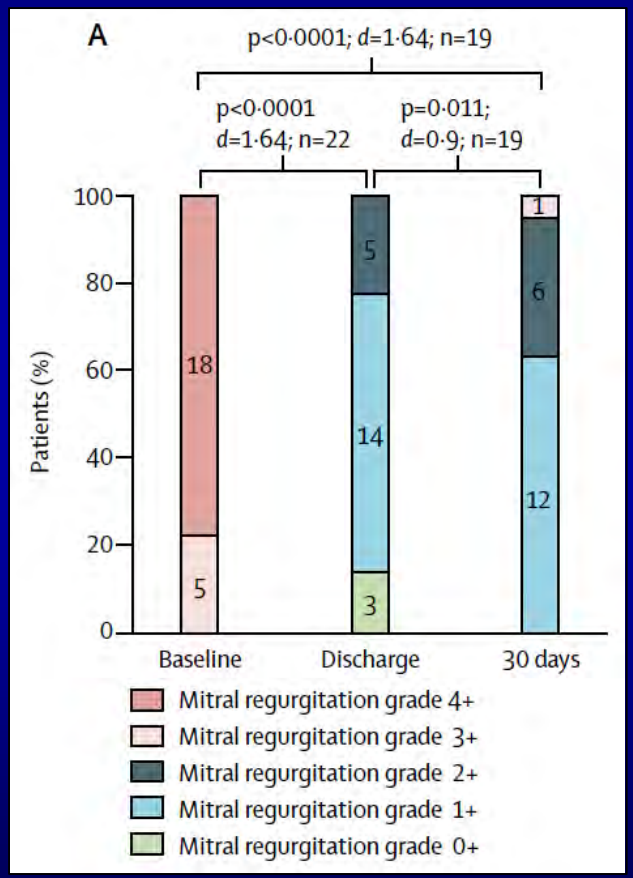
- **Leaflet specific technologies**
- Direct Annuloplasty
- Indirect/coronary sinus annuloplasty

MitraClip



Compassionate use of the PASCAL transcatheter mitral valve repair system for patients with severe mitral regurgitation: a multicentre, prospective, observational, first-in-man study

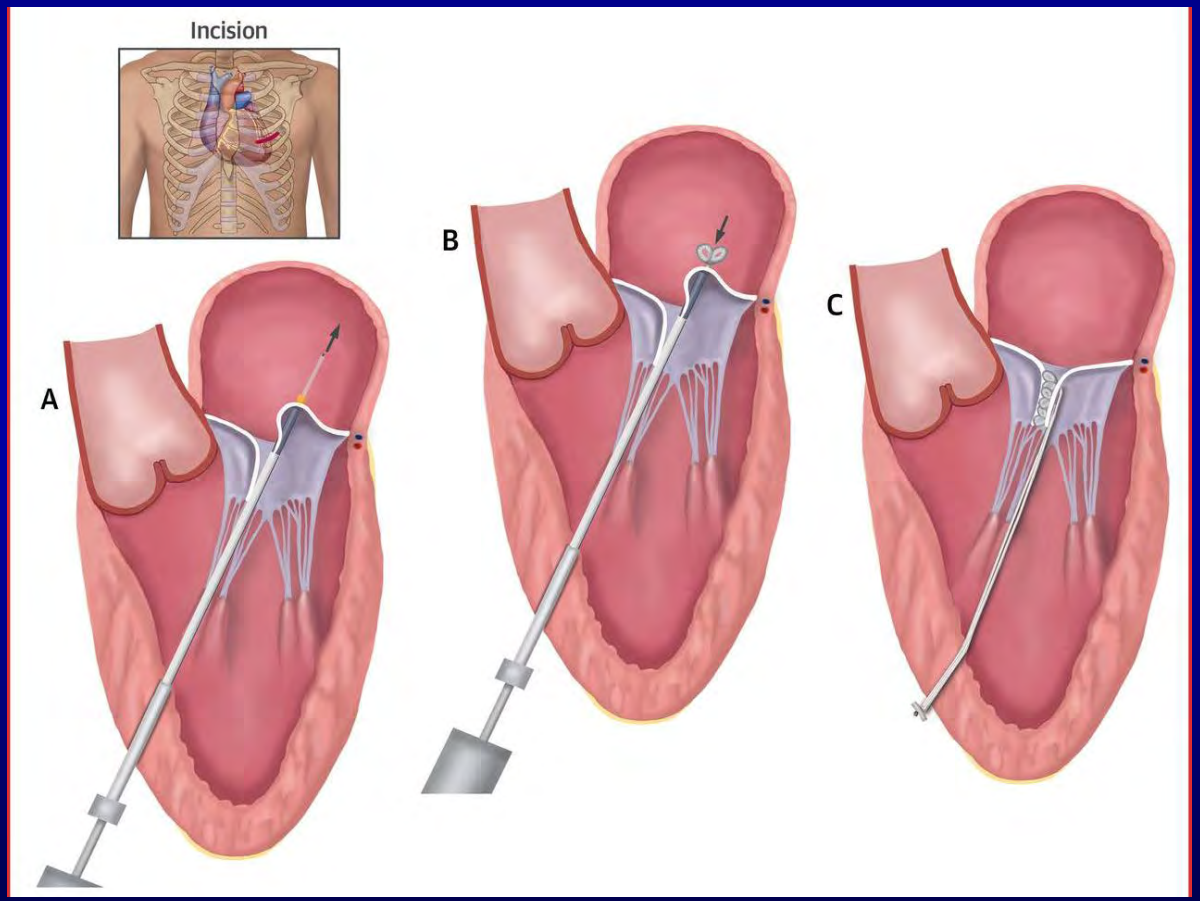




Edwards PASCAL – Edge to edge repair

Praz F. et al. Lancet 2017

Harpoon: Transcatheter chordal repair

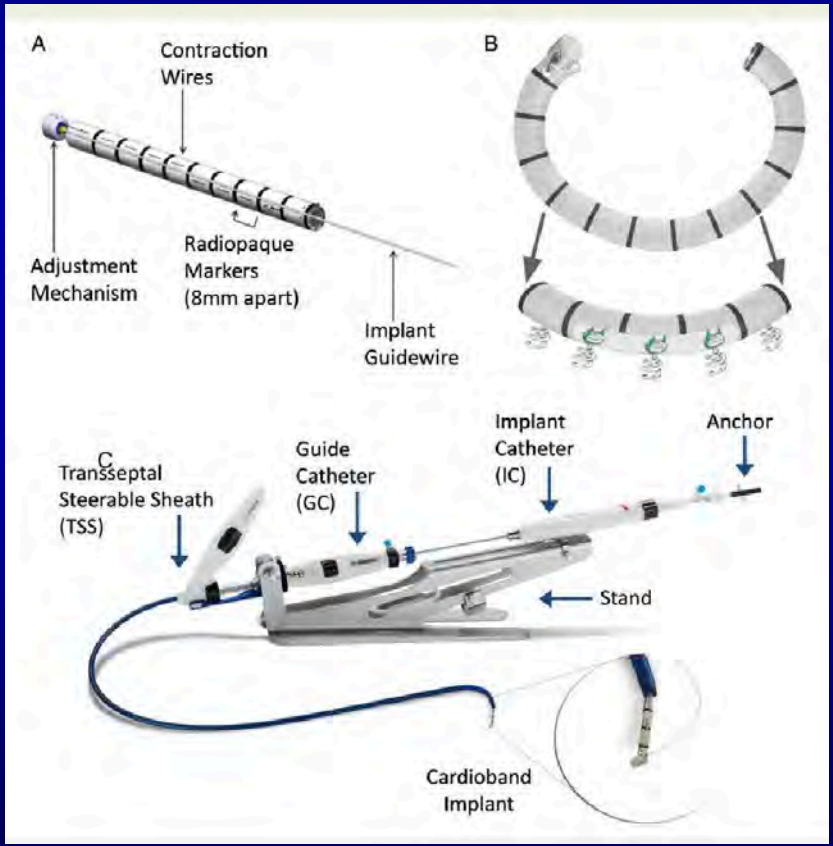


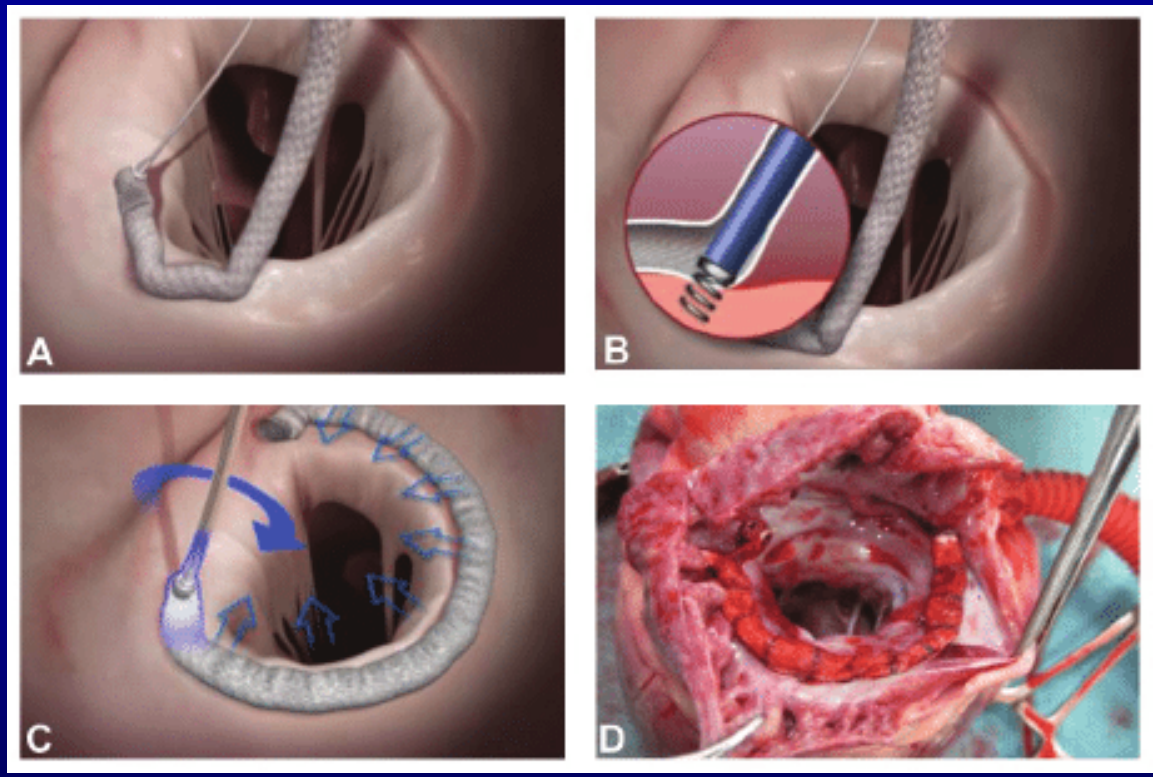
James S. Gammie. TCT 2017

Transcatheter mitral valve repair

- Leaflet specific technologies
- Direct Annuloplasty
- Indirect/coronary sinus annuloplasty

Cardioband

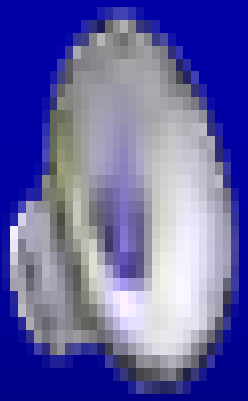

A
Contraction Wires
Adjustment Mechanism
Radiopaque Markers (8mm apart)
Implant Guidewire
B
C
Transseptal Steerable Sheath (TSS)
Guide Catheter (GC)
Implant Catheter (IC)
Anchor
Stand
Cardioband Implant

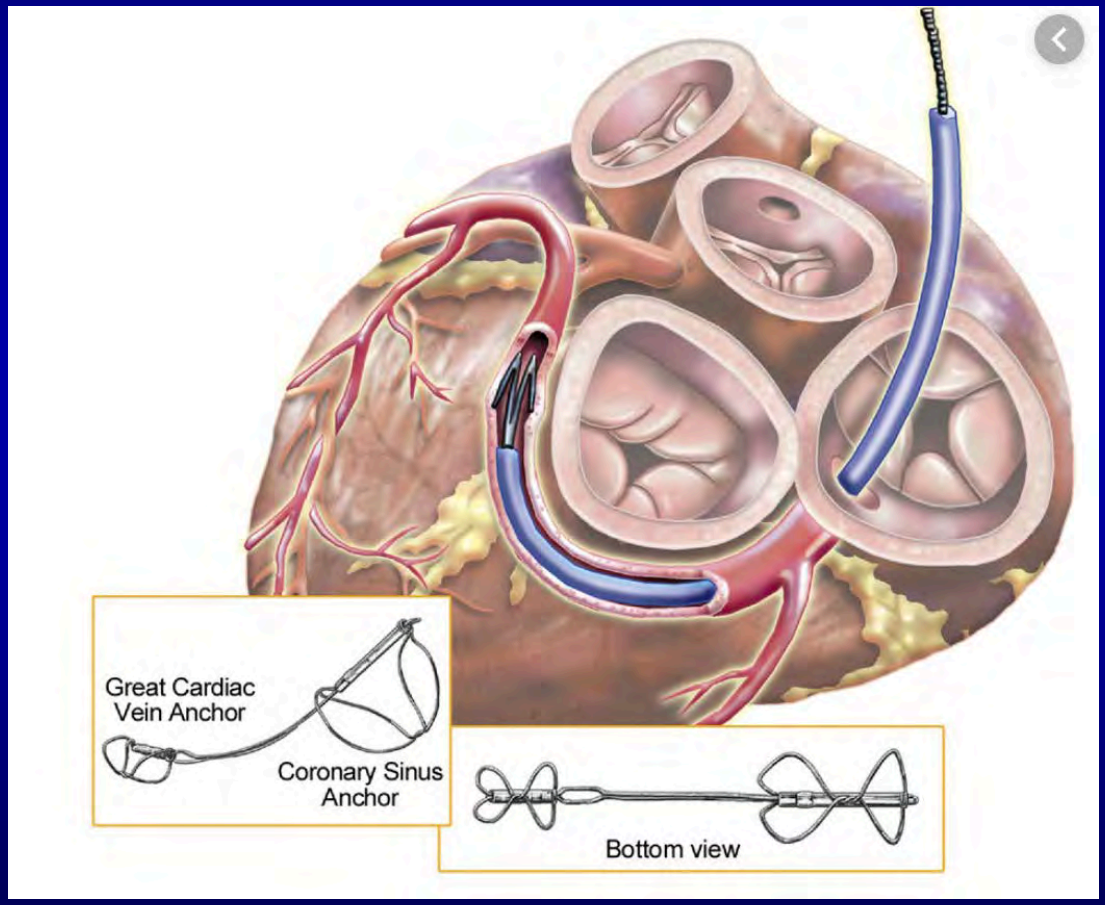

A
B
C
D

Transcatheter mitral valve repair

- Leaflet specific technologies
- Direct Annuloplasty
- Indirect/coronary sinus annuloplasty

Carillon Coronary Sinus Annuloplasty





Transcatheter mitral valve replacement

Edwards SAPIEN M3 System

Dock Delivery

SAPIEN M3 Dock

SAPIEN M3 Dock Delivery System

Valve Delivery

SAPIEN M3 Valve

Commander Delivery System

Final Implant

Primary Endpoint: Technical Success

At exit from catheterization laboratory

Primary Endpoint	% (n/N)
Technical Success	88.6 (31/35)
Alive	100 (35/35)
Successful access, delivery, and retrieval of delivery systems	91.4 (32/35)*
Deployment of devices in intended position	94.3 (33/35)**
Freedom from emergency surgery or reintervention related to the device or access procedure	97.1 (34/35)†

*One patient had separate transseptal punctures for deployment of the docking system and valve; one patient's left ventricle was too small to allow for encircling of chordae; one patient had an aortic hematoma during encircling and case was aborted
**Same as latter two cases above with unsuccessful delivery
†One patient underwent percutaneous PVL closure during the index procedure

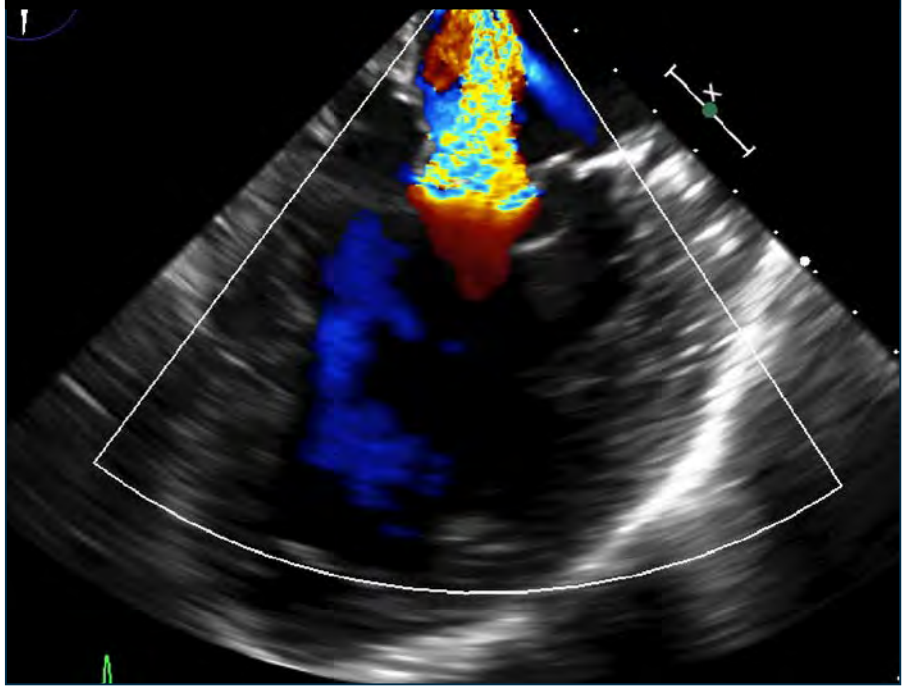
Major Adverse Events to 30 Days

Adverse Events	n (%); N=35
Freedom from Major Adverse Events	26 (74.3)
All-cause mortality	1 (2.9)
All stroke	3 (8.6)*
Disabling stroke	1 (2.9)
Myocardial infarction	0
Major cardiac structure injury	3 (8.6)
Life-threatening bleeding	0
AKI (Stage 2-3)	3 (8.6)
Hemolysis	4 (11.4)
Valve thrombosis	1 (2.9)
Device migration, embolization, or fracture	0

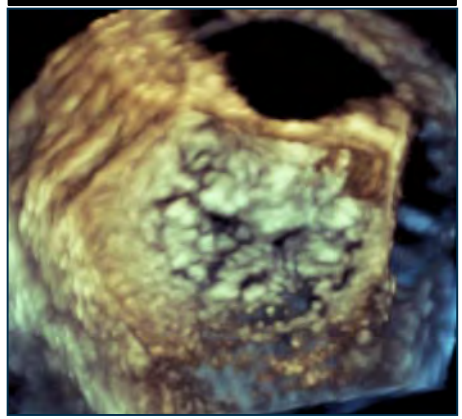
*One stroke was of unknown severity as patient expired 2 days after event

60 y/o male referred for percutaneous treatment of mitral regurgitation

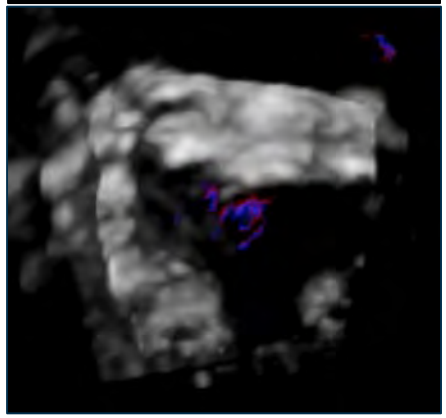
Severe Mitral regurgitation, EF 30%



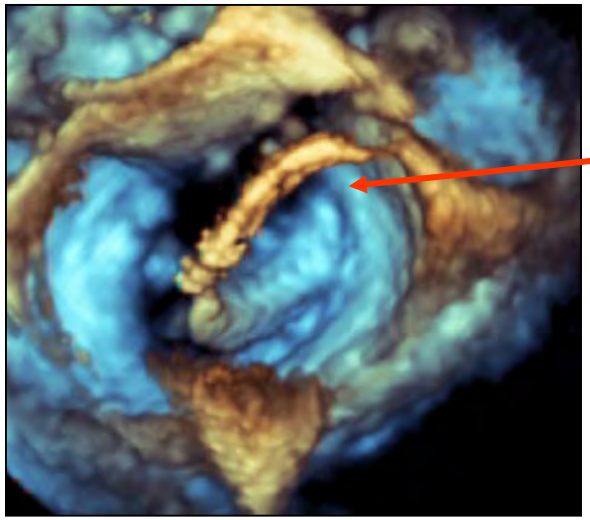
Severe restriction of posterior mitral leaflet



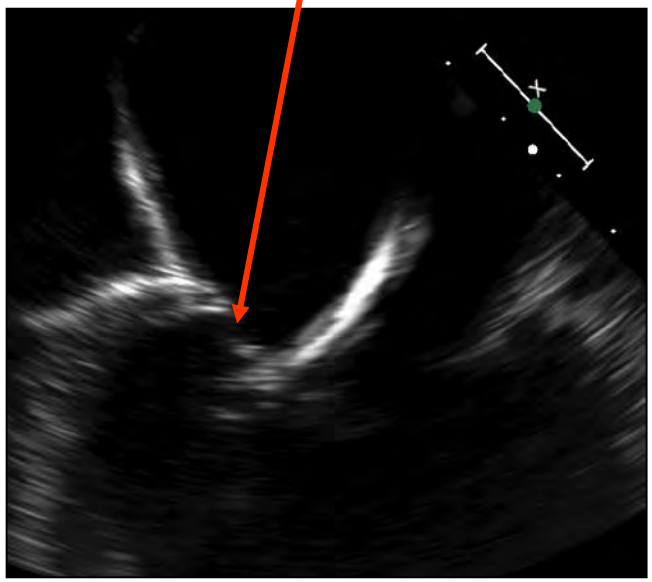
Severe central MR

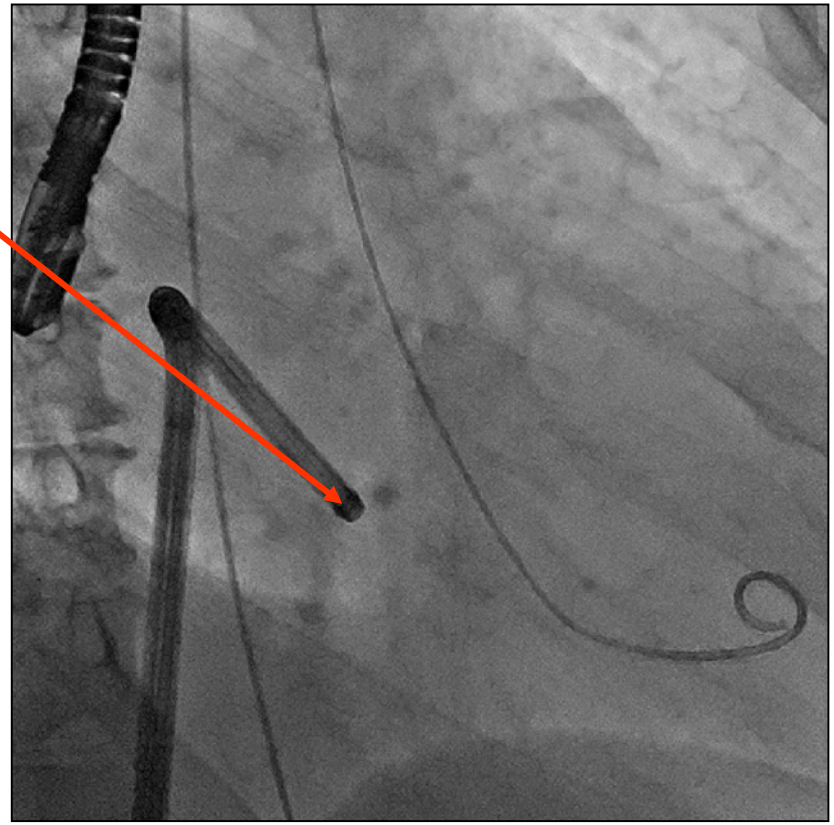


Dock delivery system advanced into the medial mitral commissure

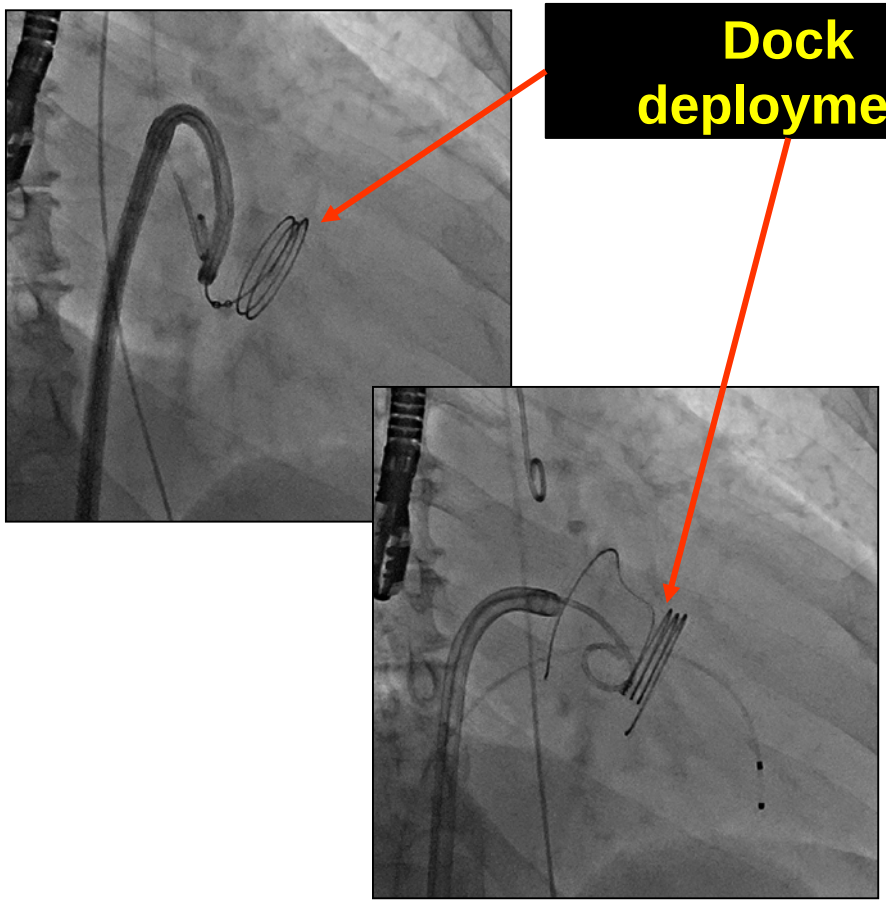


Medial commissure



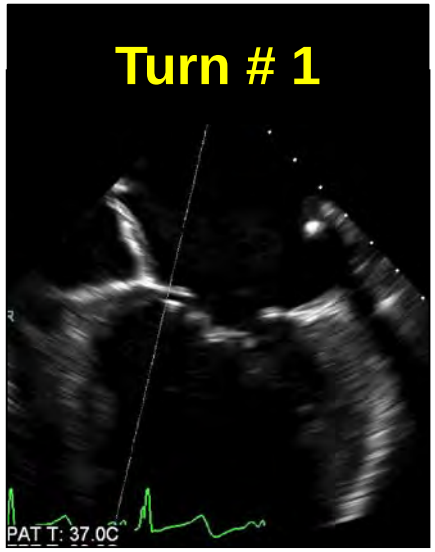


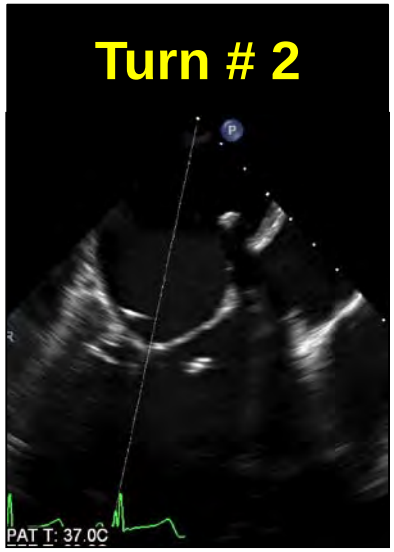
Dock deployed, under TEE guidance



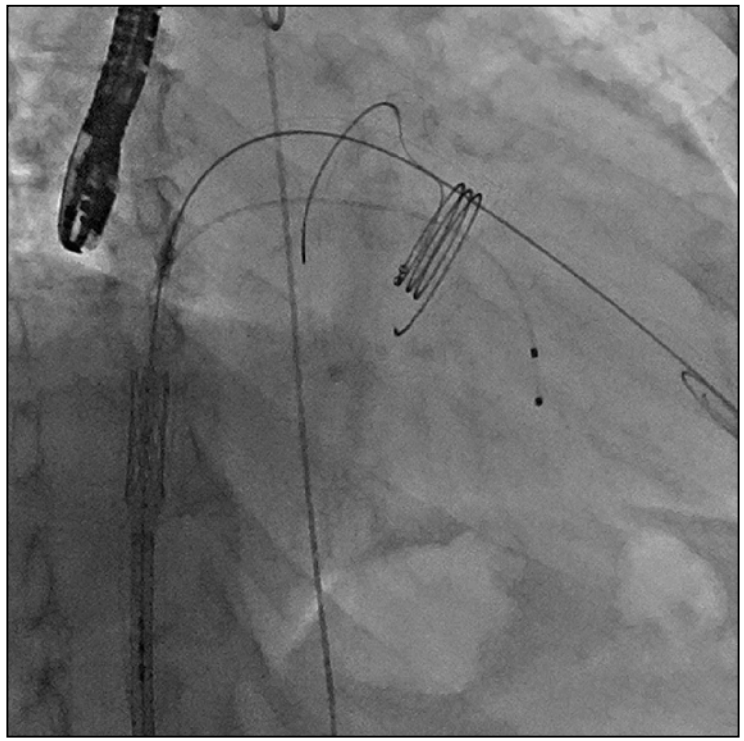
Dock deployment

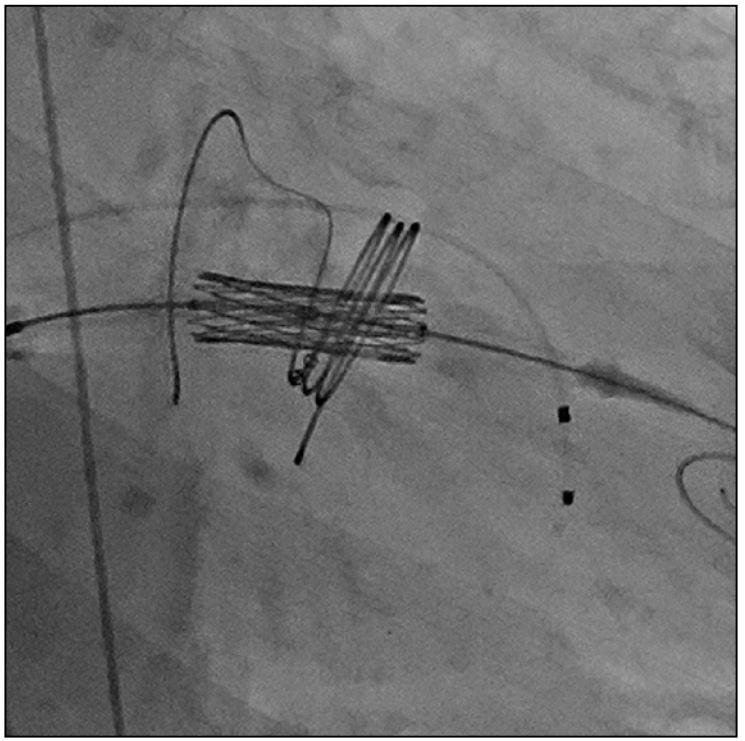
Positioning of the Dock outside the mitral chords confirmed with TEE



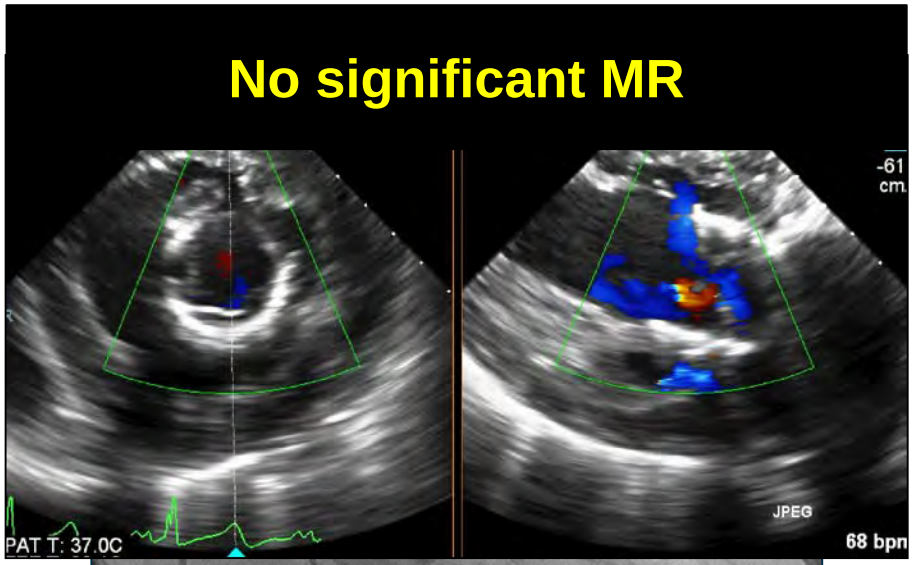


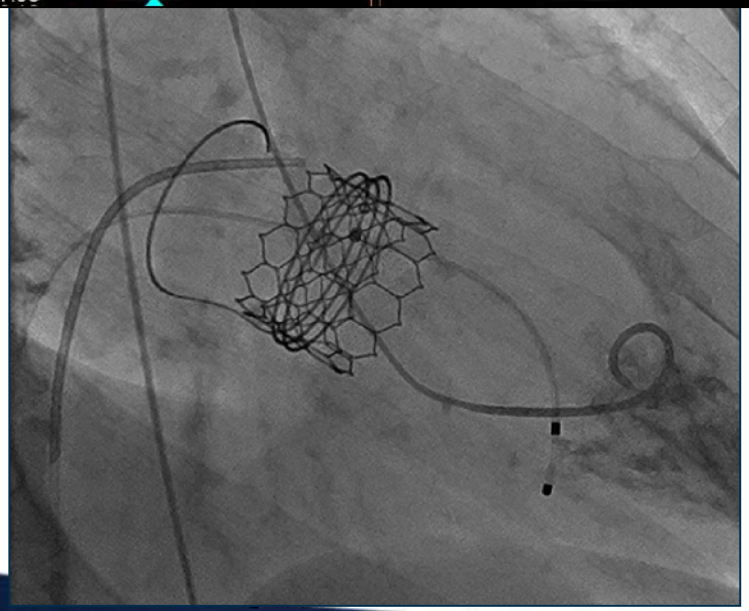
SAPIEN M3 valve deployed in the Dock, under rapid pacing

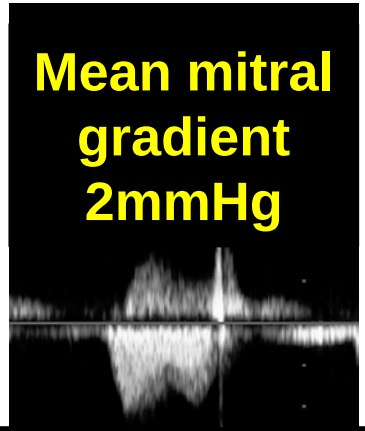


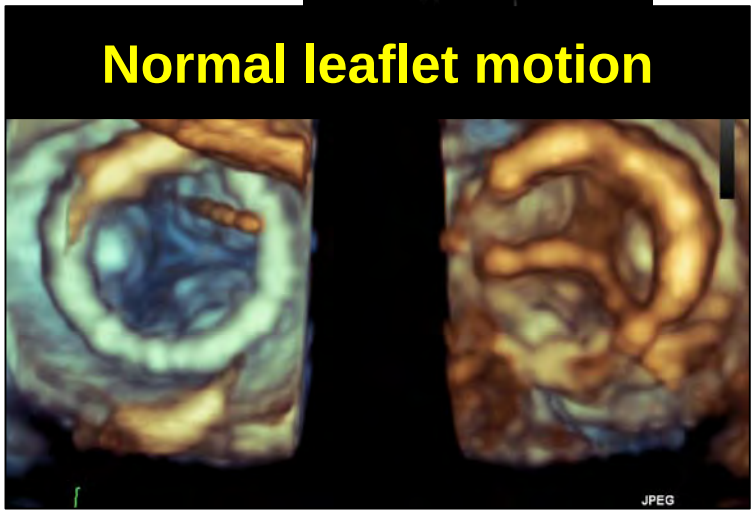


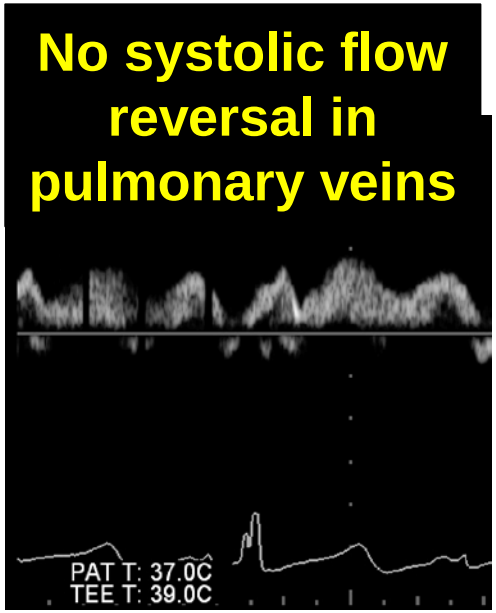
Final result s/p TMVR with 29mm SAPIEN M3











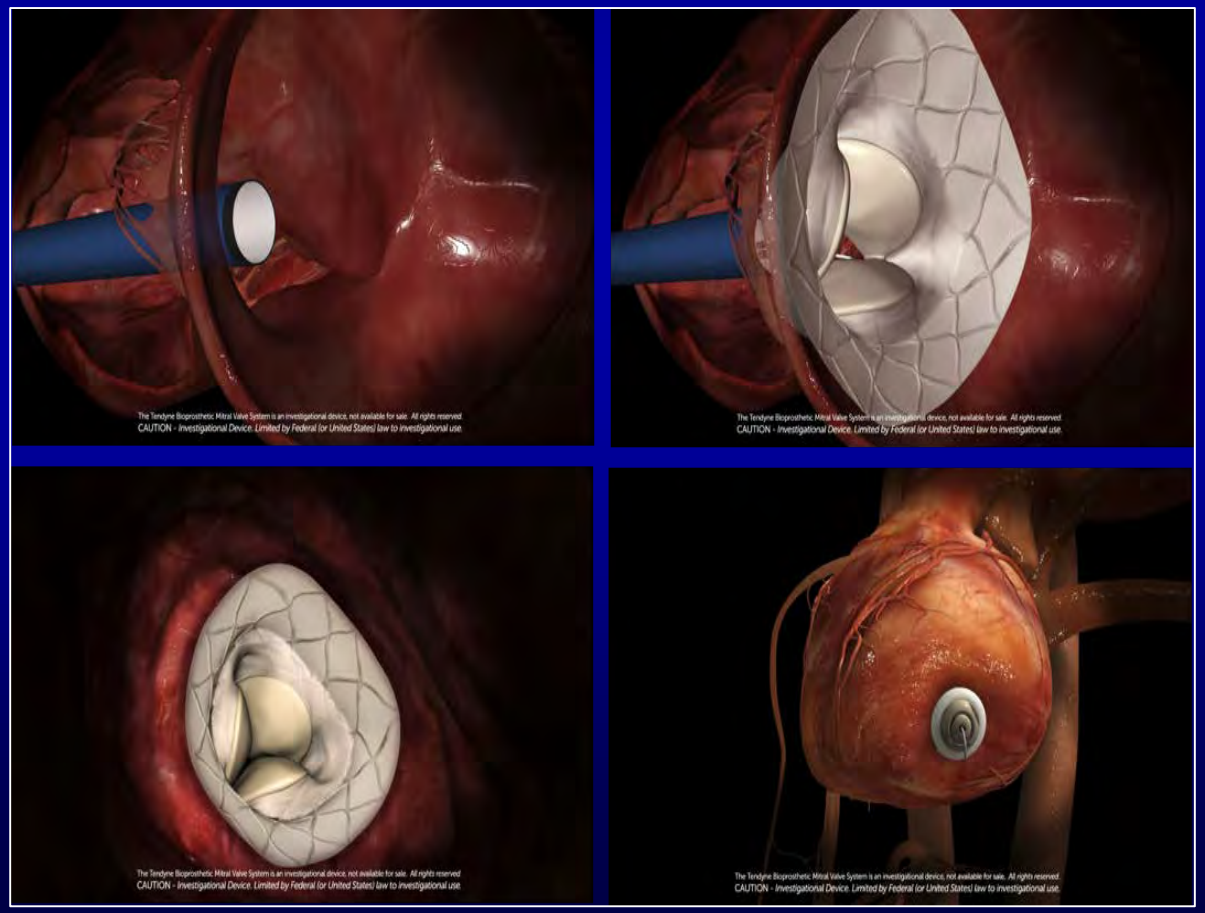
Transcatheter Mitral Valve Replacement for Patients With Symptomatic Mitral Regurgitation

A Global Feasibility Trial

Tendyne

Procedural Steps

- ✓TA Approach
- ✓Insert Catheter into LA
- ✓Intra-Annular Deployment
- ✓Ensure Valve Seating
- ✓Adjust Tether Tension
- ✓Secure Apical Pad



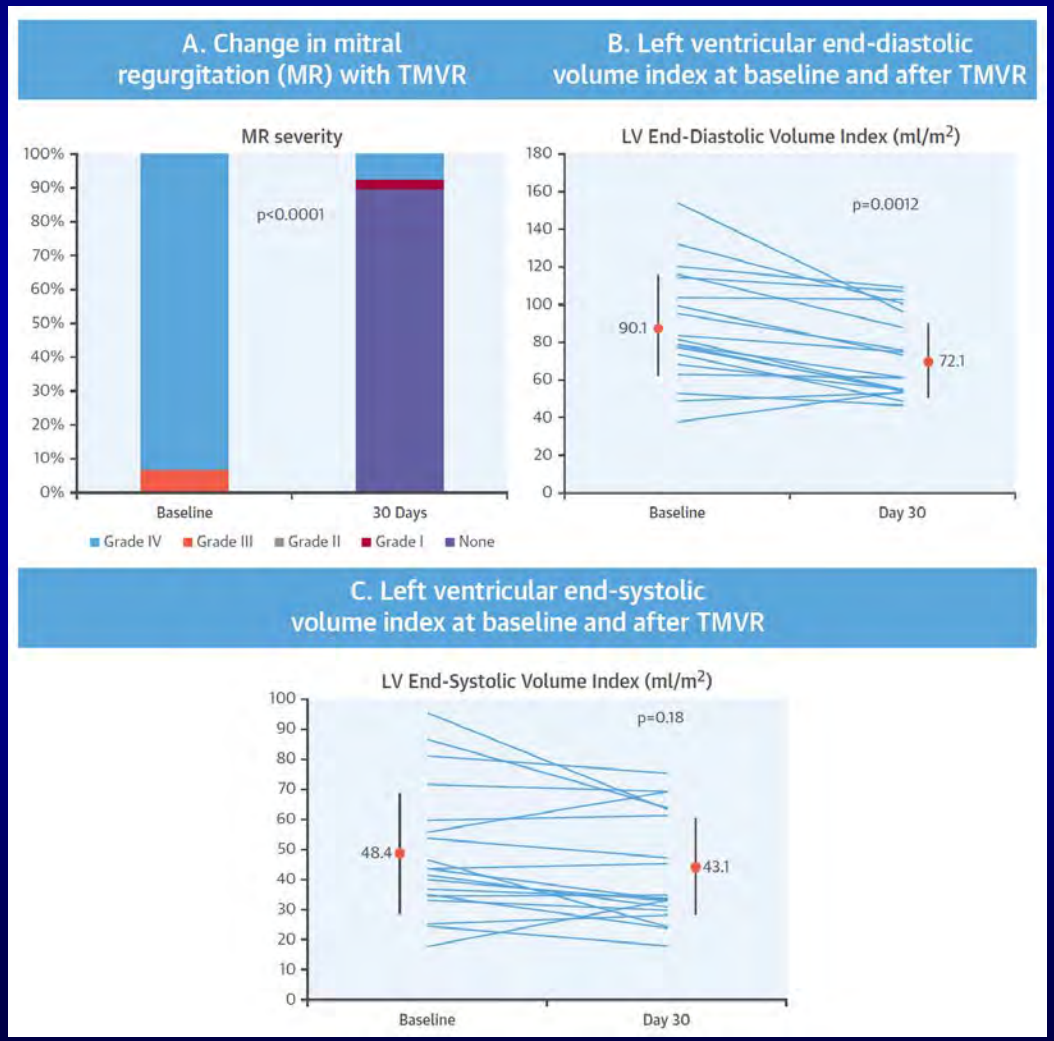
Tendyne Procedure

- ✓Fully Repositionable
- ✓Fully Retrievable
- ✓No Rapid Pacing or CPB

Transcatheter Mitral Valve Replacement for Patients With Symptomatic Mitral Regurgitation

A Global Feasibility Trial

Tendyne

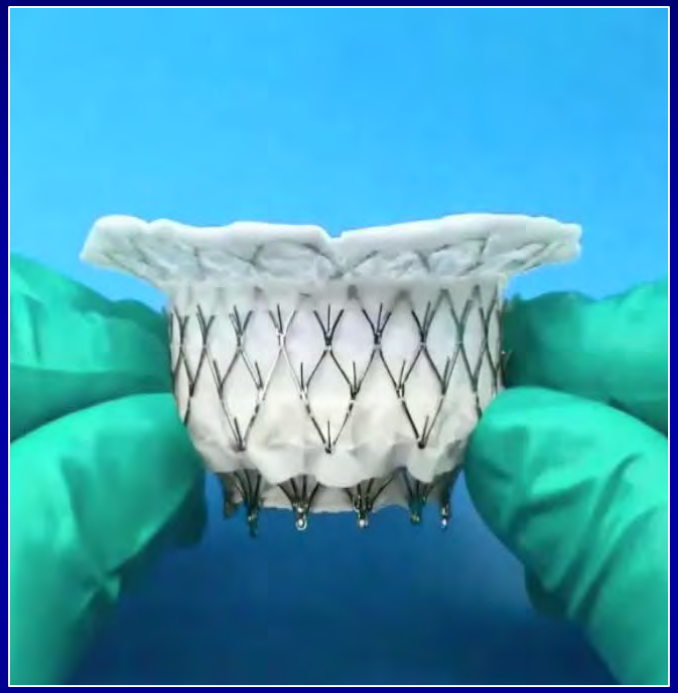


- Successful device implantation in 28 out of 30 patients
- No deaths, strokes or MIs
- Prosthetic valve thrombosis in 1 patient
- No patient with significant MR at 30 days
- Improvement in systolic and diastolic volumes

Muller D.W.M. et al. JACC 2017

Medtronic Intrepid™ TMVR

Dual-Stent system

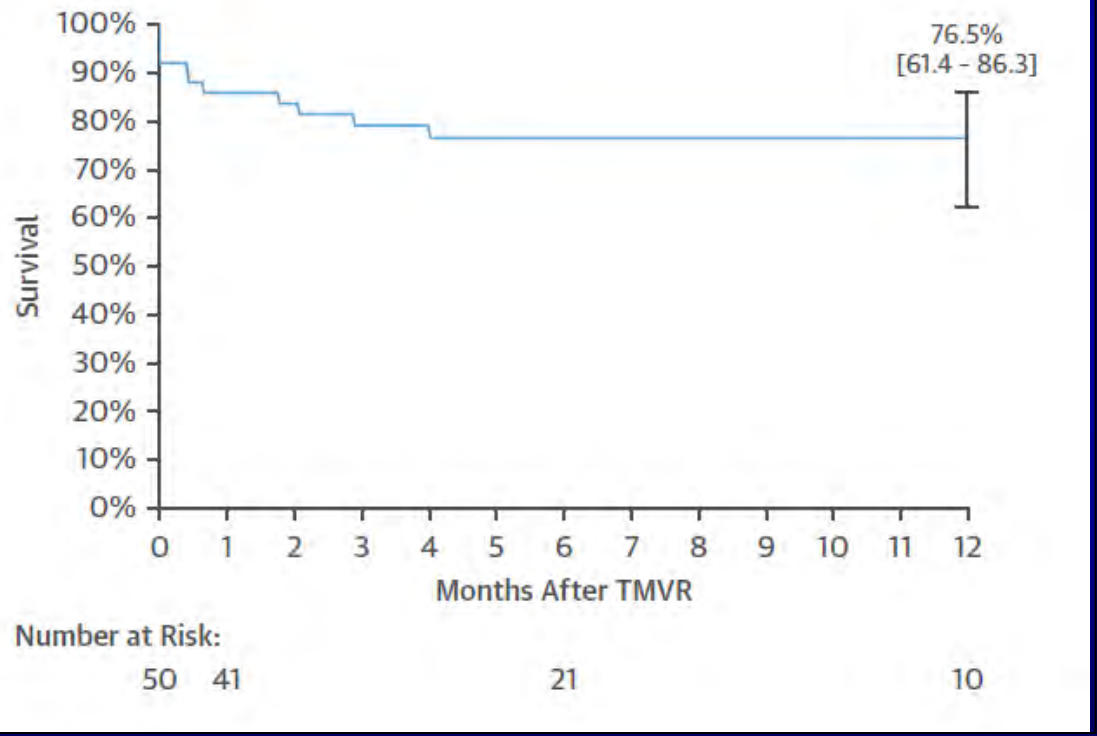


Conformable Outer Stent engages the annulus and leaflets providing fixation & sealing while isolating the inner stent from the dynamic anatomy

Circular Inner Stent houses a 27mm tricuspid bovine pericardium valve

Flexible Brim aids imaging during implantation & subsequent tissue in-growth

Early Experience With New Transcatheter Mitral Valve Replacement



50 patients undergoing TMVR with Medtronic Intrepid valve

Device implant success = 98%
No device malfunction or thrombosis
30-day mortality = 14%
Mild or no residual MR in all patients
Symptom improvement in follow-up = 79%

Bapat V. et al. JACC 2018

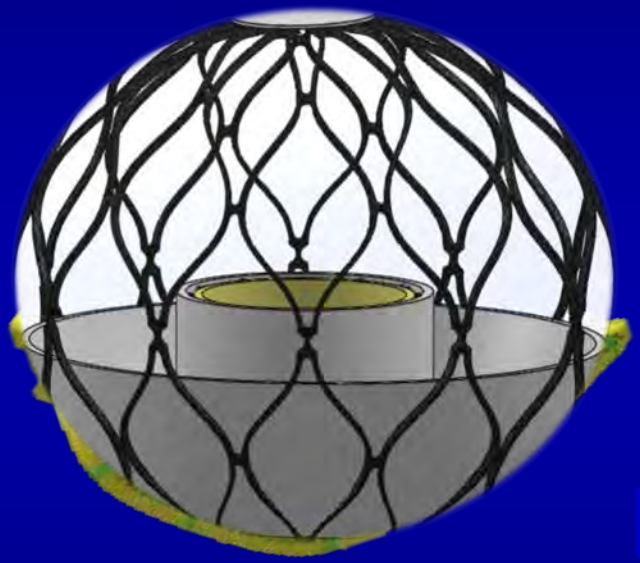
4C Implant Overview

4C Design

- *Supra Annular*
- *Atrium Only, Atraumatic Fixation*
- *Preserves native valve*

4C Differentiation

- *Native mitral annulus & valve is preserved*
- *Stops regurgitant flow – not full LV load. Less embolization risk*
- *Minimal LV footprint*



Native Mitral Annulus (Yellow)

Left Ventricle

Device

- *Flexible Self-Expanding Laser Cut Stent Frame*
- *Pericardial Tissue Valve*
- *Fabric sealing skirt*

Delivery

- *Trans-septal*
- *Trans-apical*
- *Low profile delivery systems*

Transcatheter MV Repair and Replacement: Device Landscape 2020

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

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

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

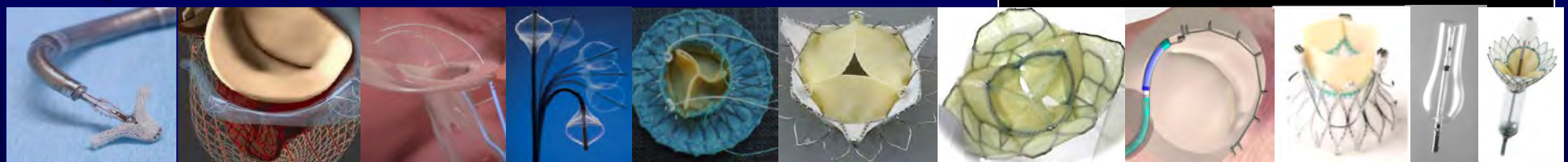
MV replacement
- Edwards CardiAQ*
- Edwards Fortis*
- Neovasc Tiara*
- Abbott Tendyne*
- Medtronic Intrepid*
- HighLife*
- MValve*
- Caison*
- NCSI NaviGate
- St. Jude
- Micro Interventional
- Valtech CardioValve
- ValveXchange
- MitrAssist
- Braile Quattuor
- Cephea
- Direct Flow
- Sinomed Accufit

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

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

Courtesy of Greg Stone. TCT 2017

*In patients *CE mark *FDA approved



Frequently performed transcatheter mitral valve interventions in 2020

- MitraClip with expanding applications
- Mitral valve in valve and valve in ring
- Valve in mitral annular calcification
- Mixed valvular heart disease

Frequently performed transcatheter mitral valve interventions in 2020

- MitraClip with expanding applications
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Transcatheter Mitral Valve Replacement for Degenerated Bioprosthetic Valves and Failed Annuloplasty Rings

BACKGROUND Limited data exist regarding transcatheter mitral valve replacement (TMVR) for patients with failed mitral valve replacement and repair.

OBJECTIVES This study sought to evaluate the outcomes of TMVR in patients with failed mitral bioprosthetic valves (valve-in-valve [ViV]) and annuloplasty rings (valve-in-ring [ViR]).

METHODS From the TMVR multicenter registry, procedural and clinical outcomes of mitral ViV and ViR were compared ac

- **Multicenter registry of 248 patients undergoing mitral valve in valve (n=172) and valve in ring (n=72)**
- **STS score 8.9%**
- **Trans-septal access 33.1%**
- **Sapien valve in 89.9%**

higher in the ViR group compared with the ViV group (28.7% vs. 12.6%; log-rank test, p = 0.01). On multivariable analysis, failed annuloplasty ring was independently associated with all-cause mortality (hazard ratio: 2.70; 95% confidence interval: 1.34 to 5.43; p = 0.005).

CONCLUSIONS The TMVR procedure provided acceptable outcomes in high-risk patients with degenerated bioprostheses or failed annuloplasty rings, but mitral ViR was associated with higher rates of procedural complications and mid-term mortality compared with mitral ViV. (J Am Coll Cardiol 2017;70:1121-31) © 2017 by the American College of Cardiology Foundation.

Yoon S. et al. JACC 2017

Transcatheter Mitral Valve Replacement for Degenerated Bioprosthetic Valves and Failed Annuloplasty Rings

TABLE 3 Procedural Outcomes

	Overall (N = 248)	ViV (n = 176)	ViR (n = 72)	p Value
Procedure-related death	3 (1.2)	2 (1.1)	1 (1.4)	>0.99
Conversion to conventional surgery	5 (2.0)	2 (1.1)	3 (4.2)	0.15
LVOT obstruction	8 (3.2)	4 (2.3)	4 (2.3)	0.18
Valve embolization	4 (1.6)	2 (1.1)	2 (2.8)	0.58
Need for second valve implantation	13 (5.1)	5 (2.8)	8 (11.1)	0.008
Left ventricular perforation	1 (0.4)	1 (0.6)	0 (0.0)	>0.99
Technical success	229 (92.3)	169 (96.0)	60 (83.3)	0.001
Re-intervention	25 (10.1)	13 (7.4)	12 (16.7)	0.03
Paravalvular leak closure	9 (3.6)	4 (2.3)	5 (6.9)	0.07
Atrial septal defect closure	10 (4.0)	7 (4.0)	3 (4.2)	0.95
Surgical mitral valve replacement	4 (1.6)	2 (1.1)	2 (2.8)	0.58
Others	2 (0.8)	0 (0.0)	2 (2.8)	0.08
Echocardiographic findings				
Mean gradient, mm Hg	6.0 ± 2.6	5.8 ± 2.7	6.4 ± 2.3	0.17
Mean gradient ≥10 mm Hg	16 (6.5)	11 (6.3)	5 (6.9)	0.84
Mitral valve area, cm^2	2.1 ± 0.8	2.1 ± 0.8	2.0 ± 0.6	0.37
LVEF, %	50.3 ± 13.6	52.8 ± 12.0	44.1 ± 15.4	<0.001
Mitral regurgitation moderate or higher after procedure	26 (10.3)	12 (6.8)	14 (19.4)	0.003
Mitral regurgitation moderate or higher at 30 days*	15 (6.5)	6 (3.6)	9 (13.6)	0.005
Device success (modified)	212 (85.5)	157 (89.2)	55 (76.4)	0.009

Multicenter registry of 248 patients undergoing mitral valve in valve (n=172) and valve in ring (n=72)

- **Procedural mortality…... 1.2%**
- **Conversion to surgery…. 2.0%**
- **Need for 2nd valve…… 5.1%**
- **Mean gradient……..6mmHg**

Yoon S. et al. JACC 2017

Transcatheter Mitral Valve Replacement for Degenerated Bioprosthetic Valves and Failed Annuloplasty Rings

TABLE 4 Clinical Outcomes

	Overall (n = 248)	ViV (n = 176)	ViR (n = 72)	p Value
All-cause mortality at 30 days	16 (6.5)	10 (5.7)	6 (8.3)	0.44
Stroke	4 (1.6)	4 (2.3)	0 (0.0)	0.33
Bleeding				
Major or extensive	14 (5.6)	11 (6.3)	3 (4.2)	0.52
Life-threatening or fatal	10 (4.0)	4 (2.3)	6 (8.3)	0.03
Major vascular complication	4 (1.6)	3 (1.7)	1 (1.4)	>0.99
Acute kidney injury (stage 2 or 3)	15 (6.0)	7 (4.0)	8 (11.1)	0.03
Procedure success	182 (73.4)	140 (79.5)	42 (58.3)	0.001
All-cause mortality at 1 year*	33 (16.9)	18 (12.6)	15 (28.7)	0.01

Multicenter registry of 248 patients undergoing mitral valve in valve (n=172) and valve in ring (n=72)

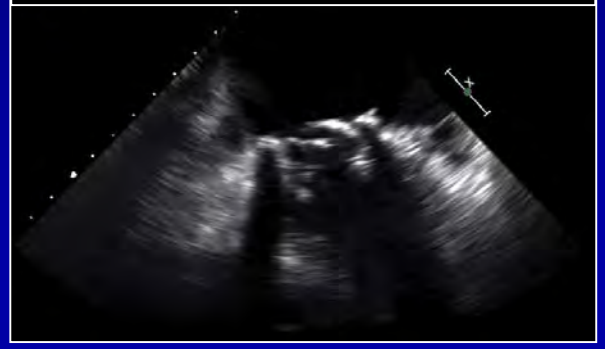
- **30-day mortality……...6.5%**
- **Stroke……1.6%**
- **1-year mortality……..16.9%**

Yoon S. et al. JACC 2017

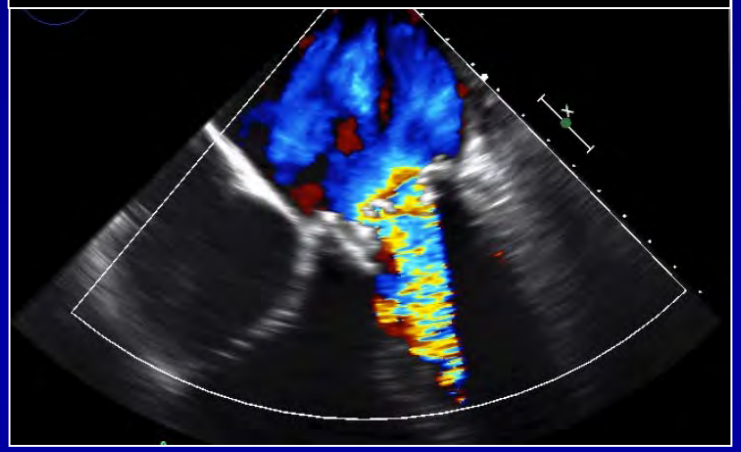
78 y/o male referred for mitral valve in valve

Degenerative Mosaic mitral valve with flail leaflet and severe central and paravalvular MR

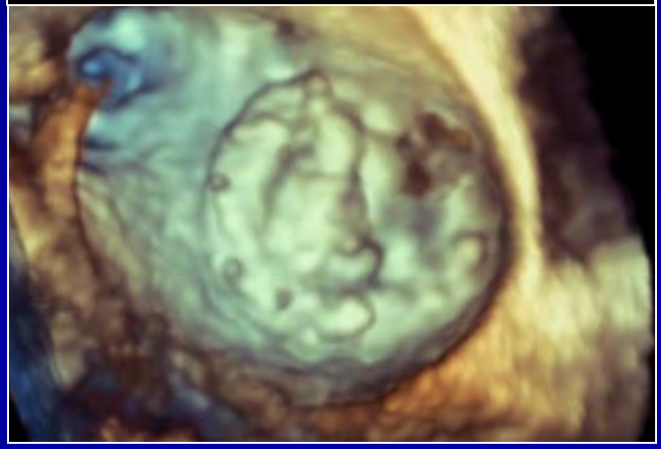
Flail of Mosaic mitral valve



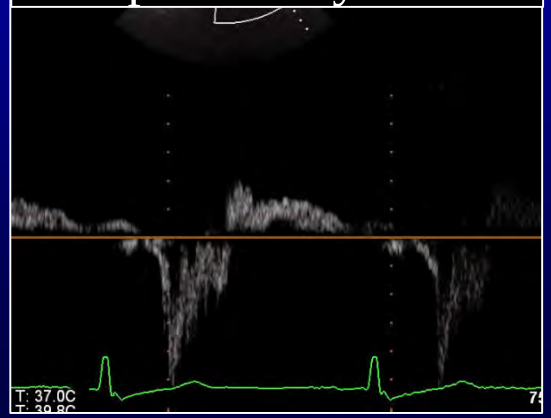
Severe central MR



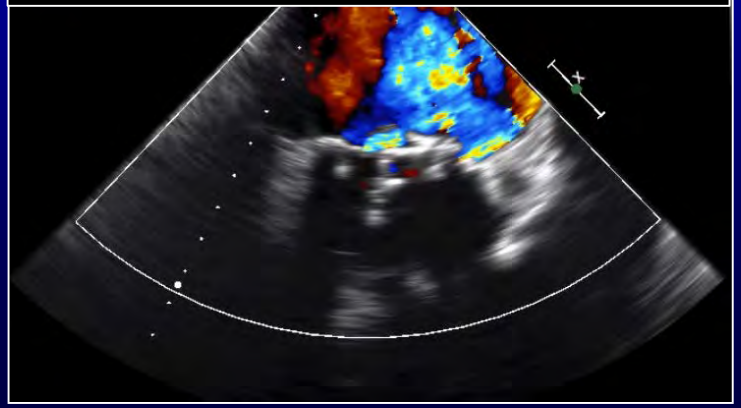
Thickened and restricted mitral valve leaflets



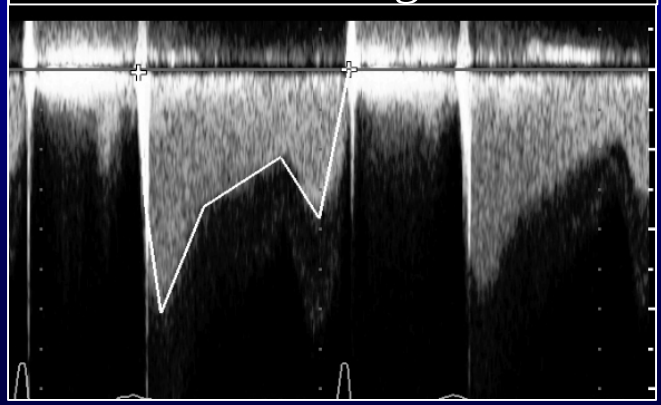
Systolic flow reversal of pulmonary veins



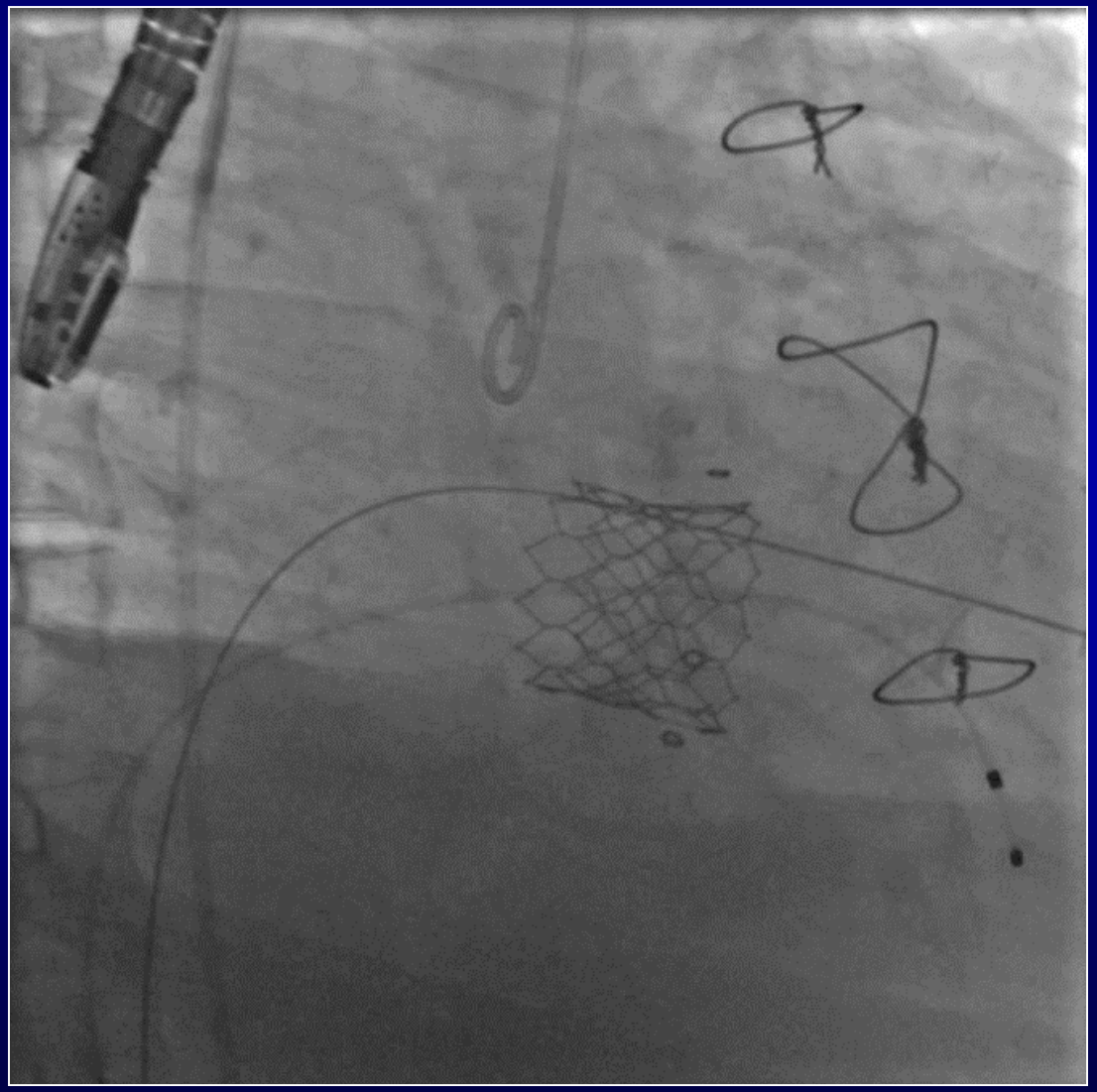
Severe paravalvular MR



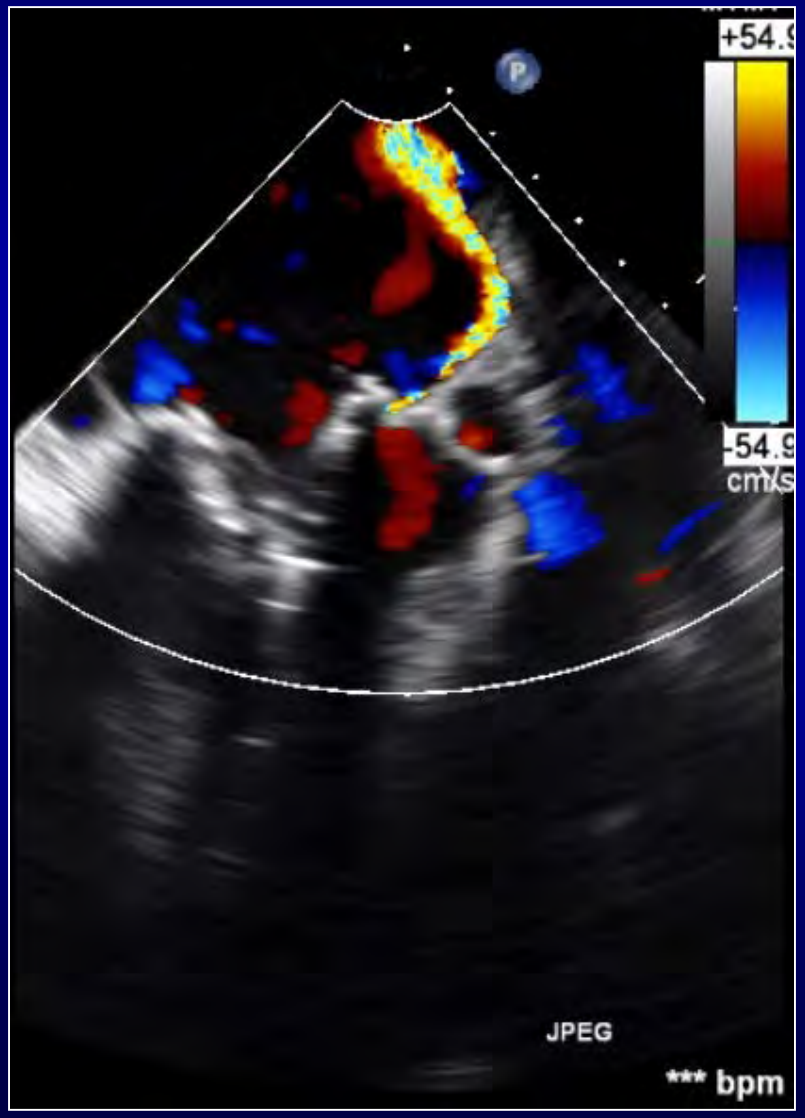
Mean mitral valve gradient 8mmHg

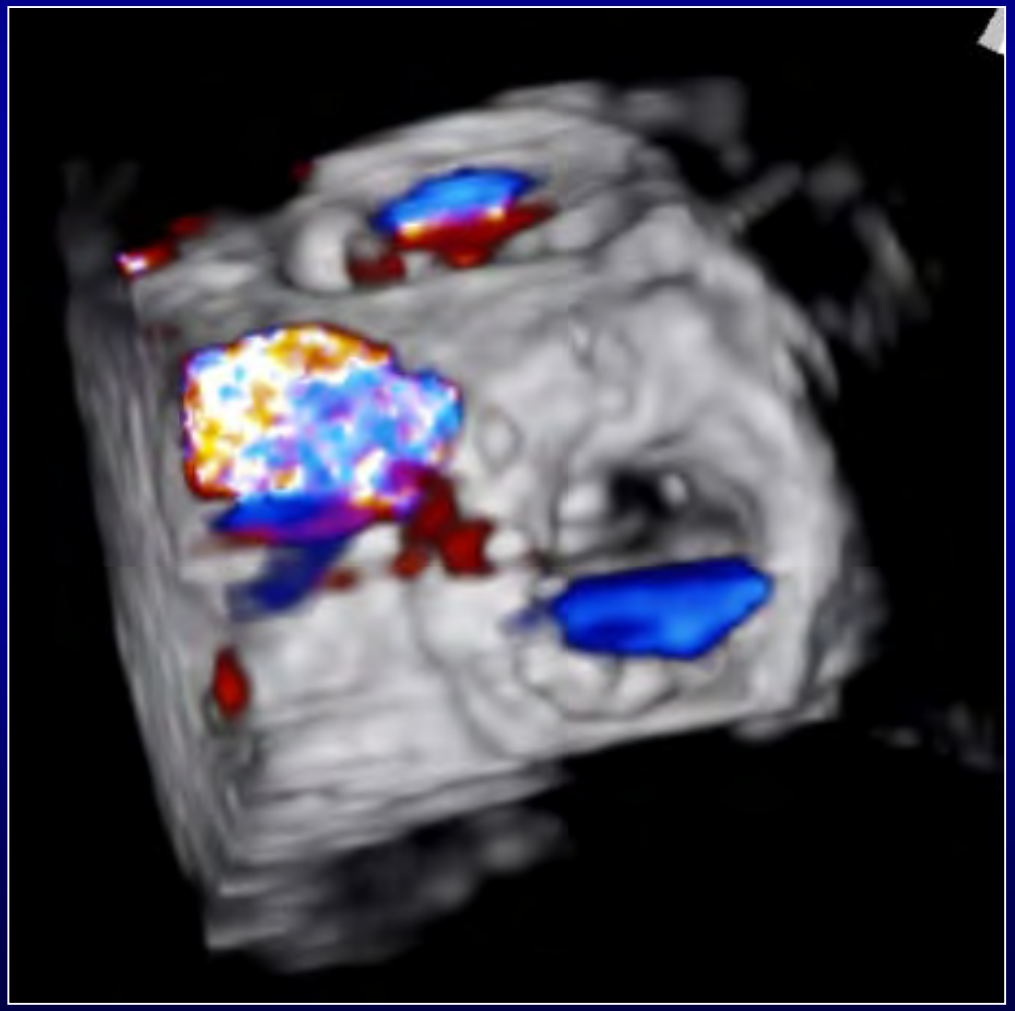


Trans-septal mitral ViV performed with a 29mm Sapien 3 valve

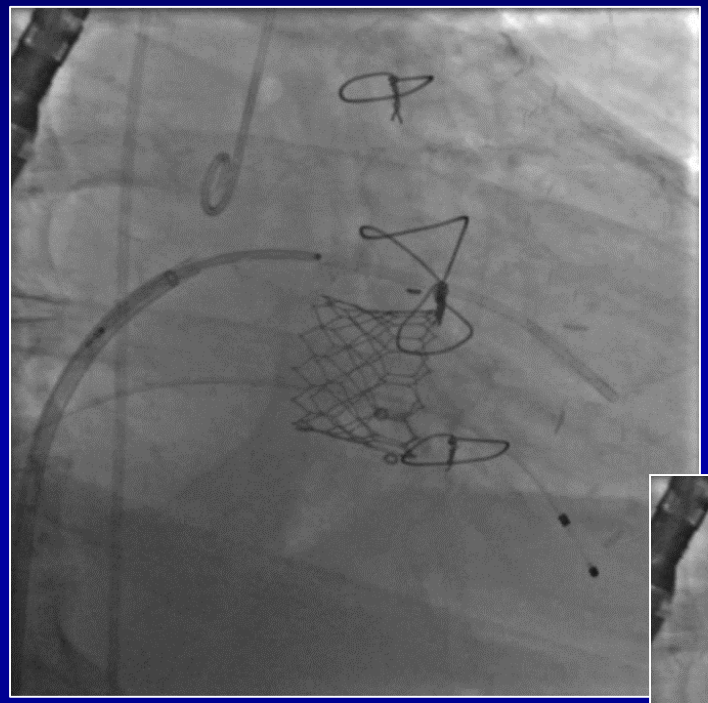


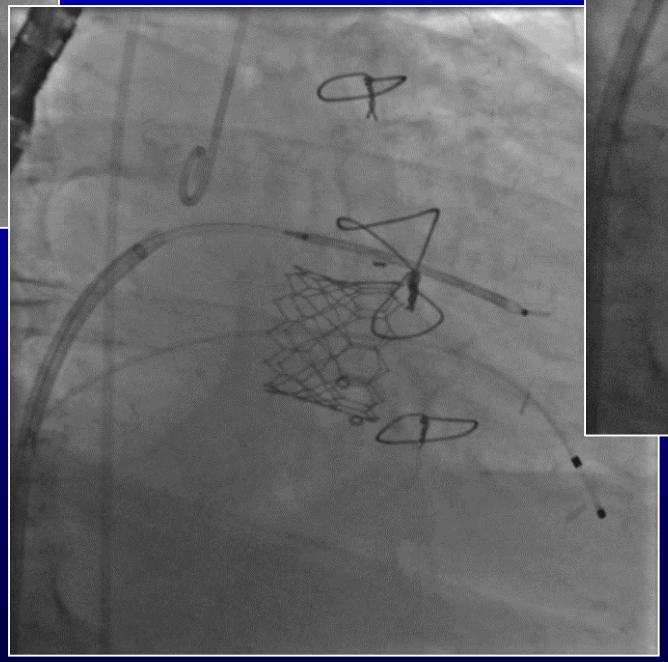
s/p mitral ViV with 29mm Sapien 3
No central MR; residual severe paravalvular MR





12mm AVP2 plug deployed in the paravalvular space

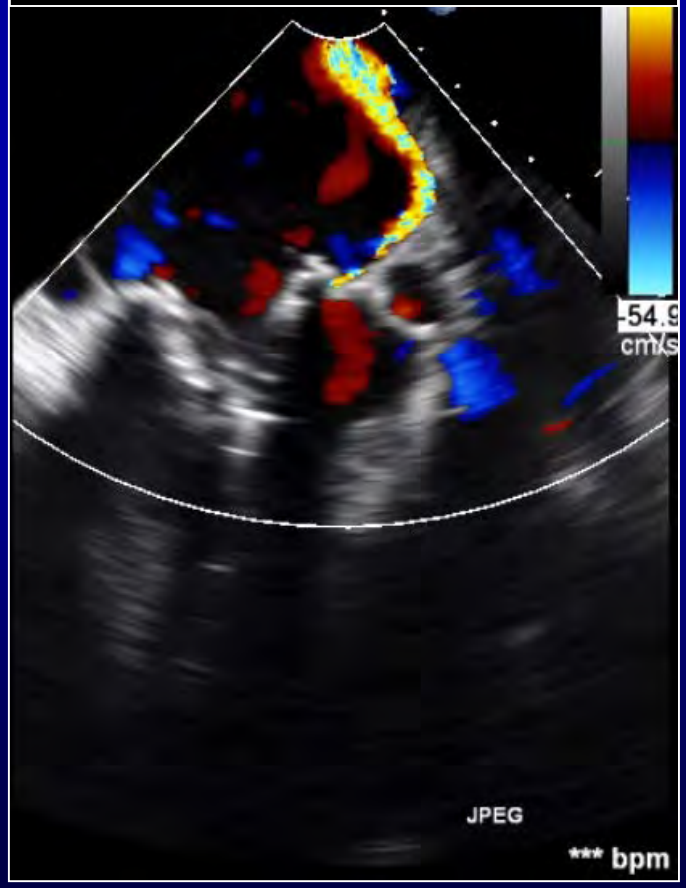




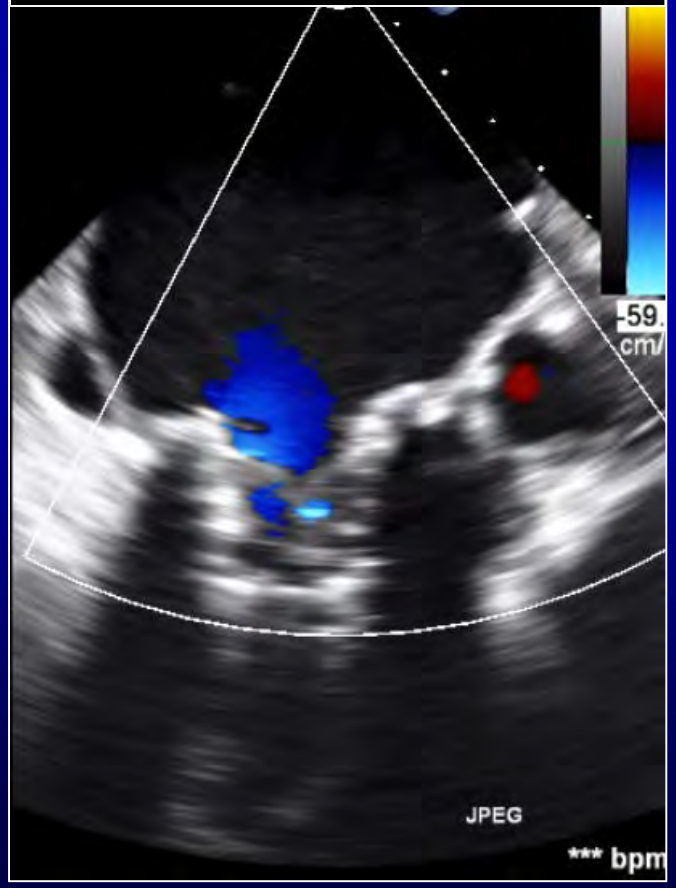
s/p paravalvular leak closure with 12mm AVP2 plug

No significant paravalvular MR

Severe PVL



Trivial PVL after PVL closure



Frequently performed transcatheter mitral valve interventions in 2020

- MitraClip with expanding applications
- Mitral valve in valve and valve in ring
- Valve in mitral annular calcification
- Mixed valvular heart disease

1-year outcomes of Transcatheter Mitral Valve Replacement in Native Mitral Valve Disease With Severe Mitral Annular Calcification

Update from the first global registry

- 116 patients from 51 centers in 11 countries
- Patient with severe mitral annular calcification undergoing TMVR with transcatheter aortic valve

Procedural outcomes	n (%)
Technical success by MVARC criteria	89 (76.7%)
LVOT obstruction with hemodynamic compromise	13 (11.2%)
Valve embolization	5 (4.3%)
Need for second valve (migration=6, MR=11)	17 (14.7%)
LV perforation	2 (1.7%)
Conversion to open surgery (embolization=2, LV perforation=1, LVOTO=1)	4 (3.4%)

Guerrera M. et al. Manuscript accepted in JACC 2018

1-year outcomes of Transcatheter Mitral Valve Replacement in Native Mitral Valve Disease With Severe Mitral Annular Calcification

Update from the first global registry

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- Patient with severe mitral annular calcification undergoing TMVR with transcatheter aortic valve

Outcomes	30 Days n=116	1 Year n=106
All-Cause Mortality	29 (25%)	58 (54.7%)
Cardiovascular death	15 (13%)	26 (24.5%)
Non-Cardiac death	14 (12%)	32 (30.2%)

Guerrera M. et al. JACC 2018

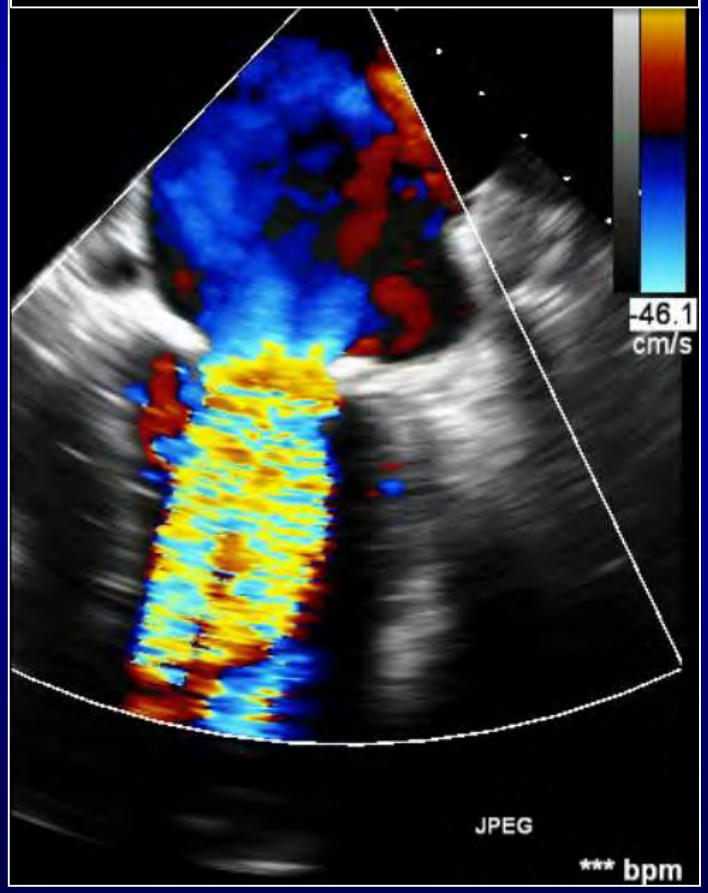
49 y/o female referred for percutaneous management of mitral and aortic valve disease

- Severe mitral stenosis and moderate-severe mitral regurgitation
- Diastolic congestive heart failure, NYHA III
- Severe pulmonary hypertension, on supplemental oxygen at night, 2 L
- End stage renal disease, on hemodialysis
- Thrombocytopenia (platelet count 80)
- Occluded SVC
- Central retinal occlusion
- Transient ischemic attack
- Diabetes mellitus
- Frequent pneumonias
- Frailty

Patient deemed inoperable for surgical valve replacement

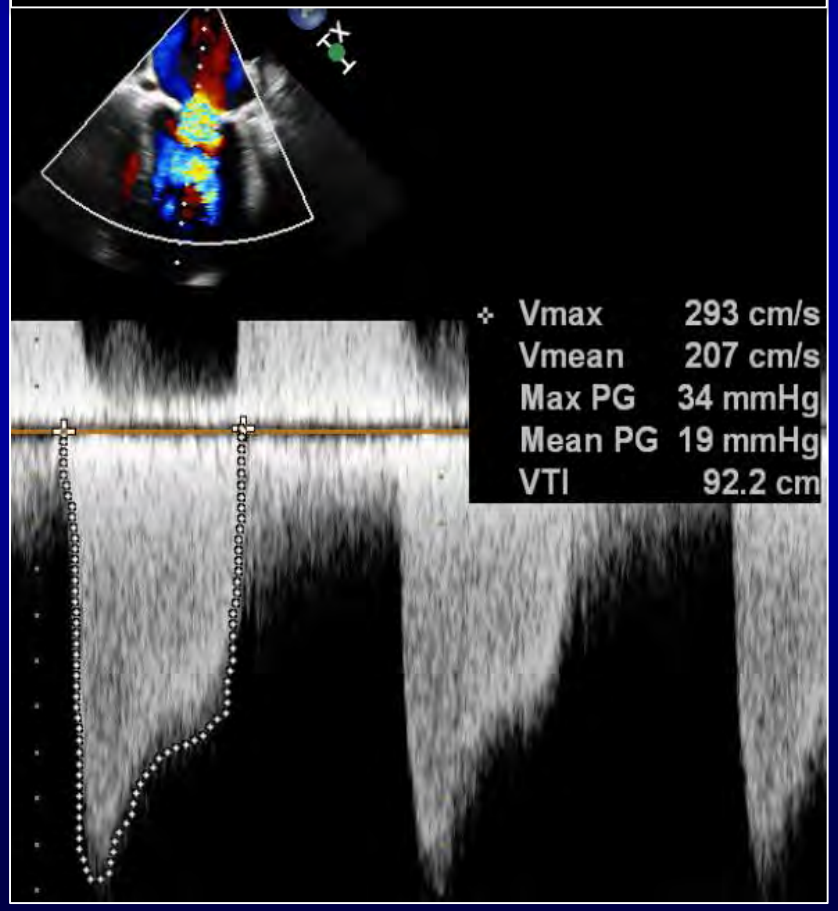
Severe mitral stenosis and moderate mitral regurgitation

Moderate-severe MR

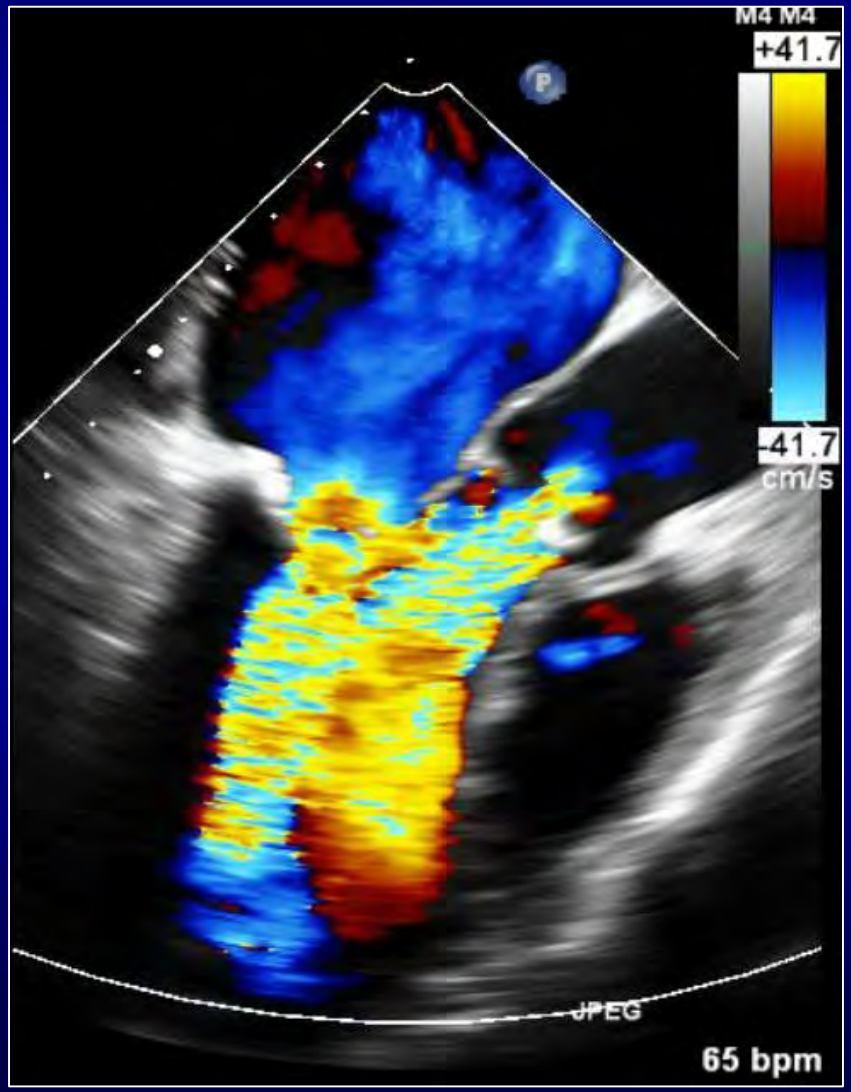


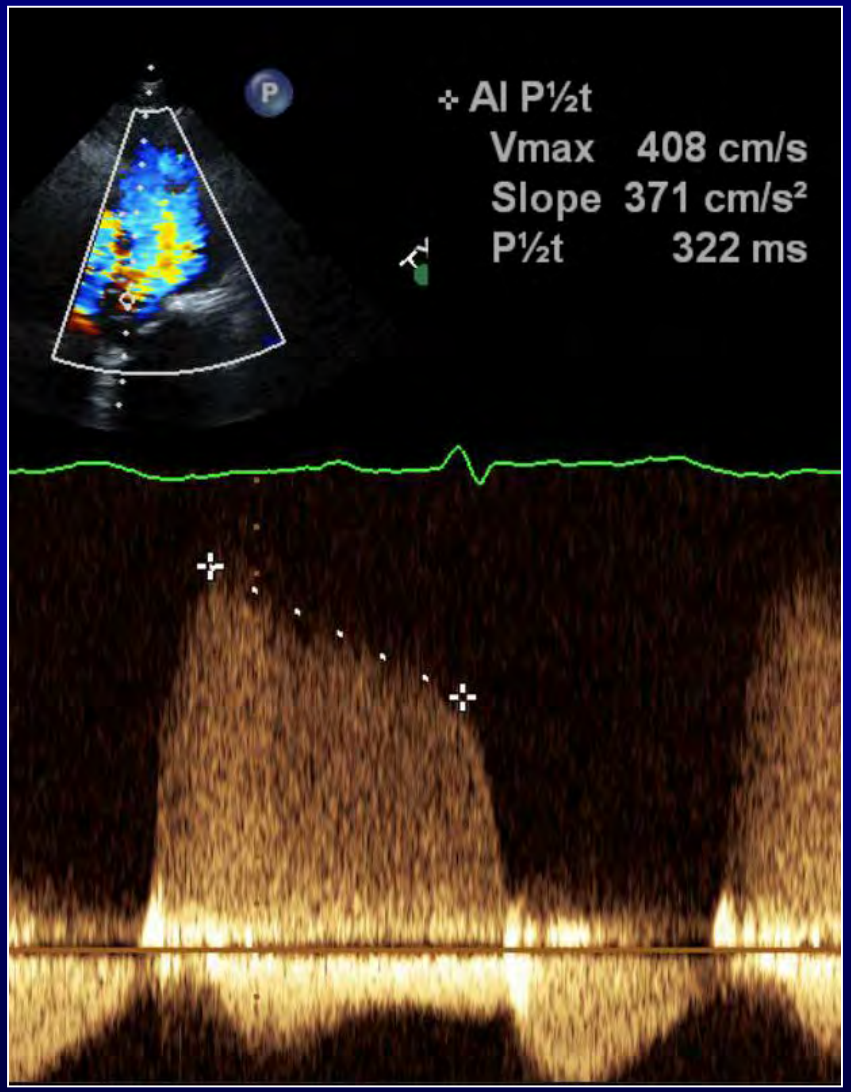
Severely restricted mitral valve leaflets with severe MAC

Severe mitral stenosis

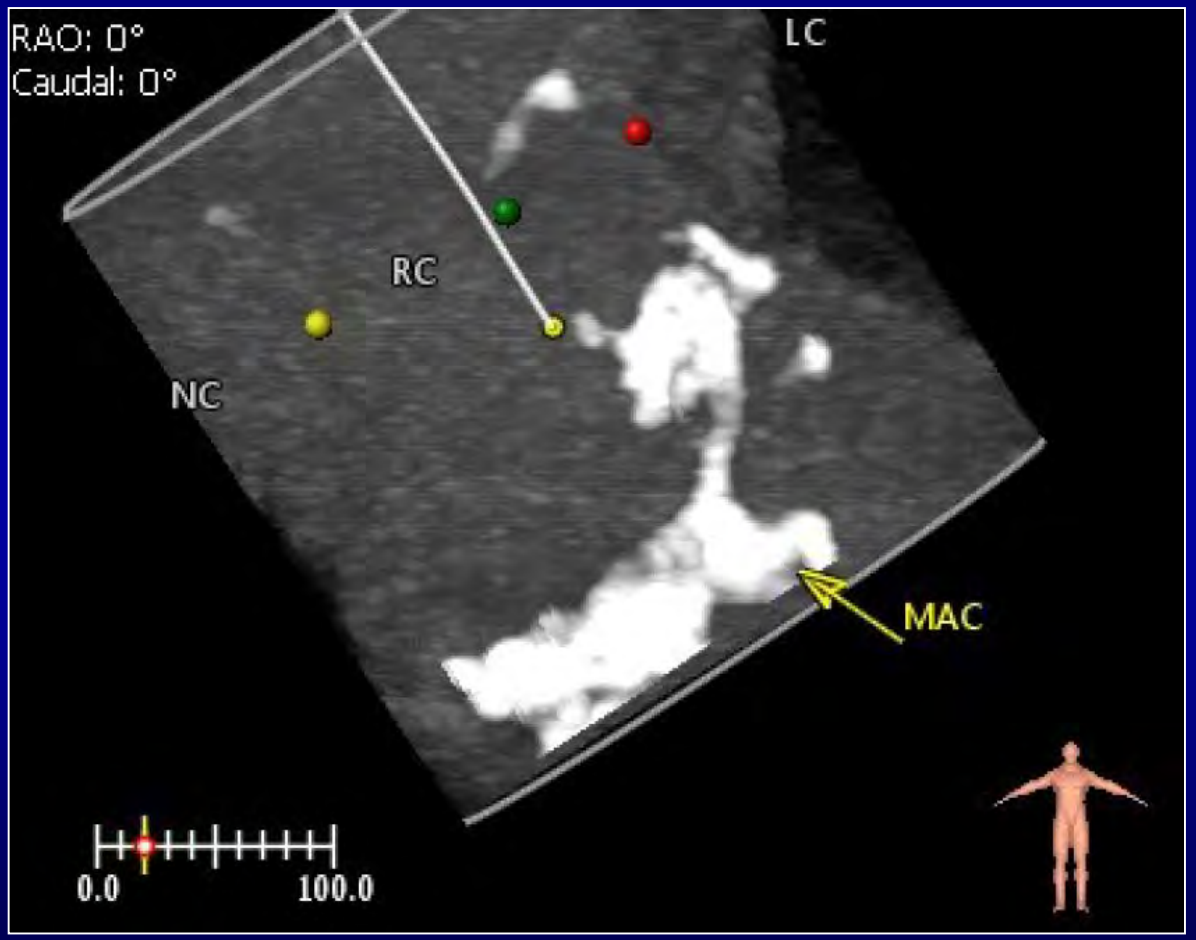


Coexisting moderate-severe AR



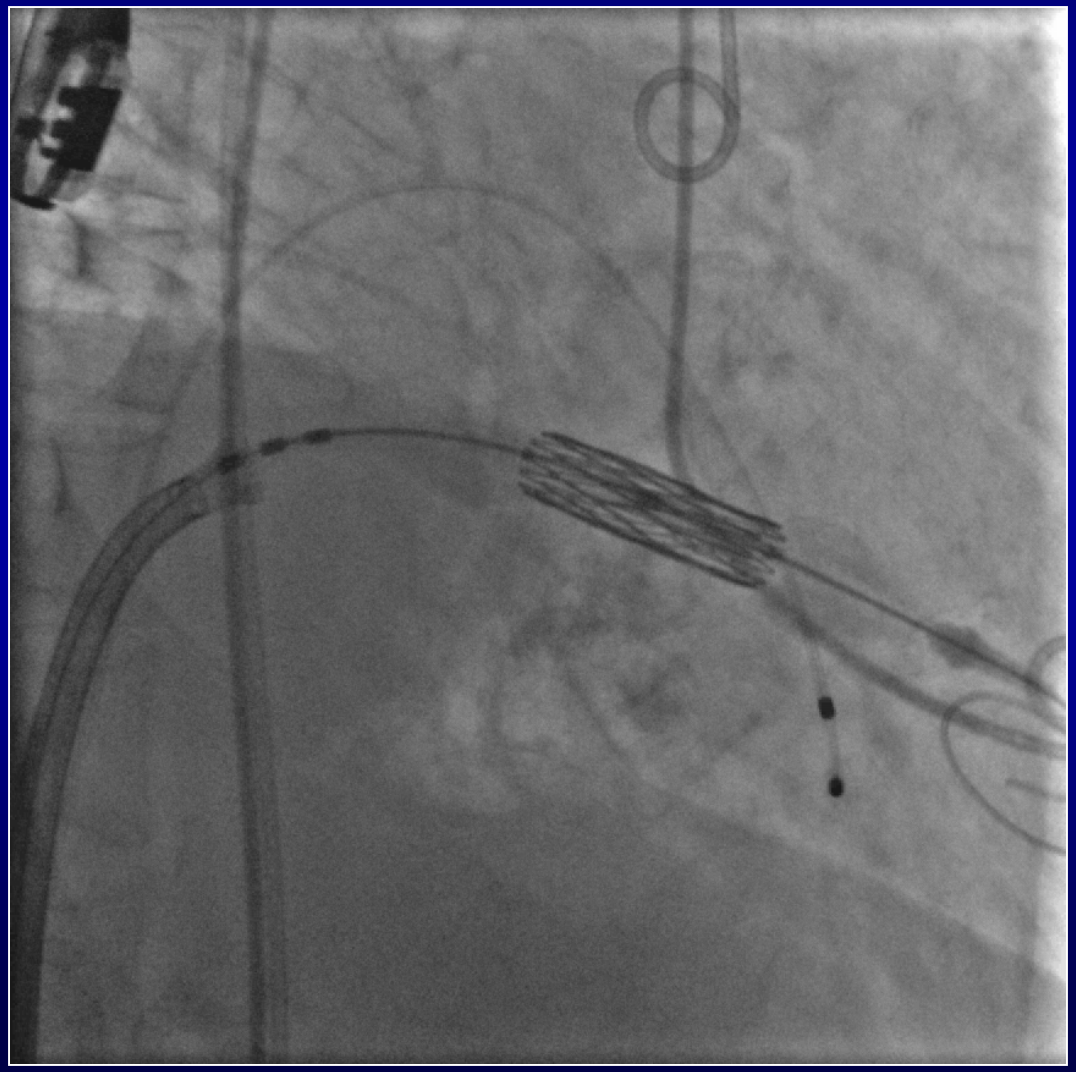


Mitral annular calcification on CT

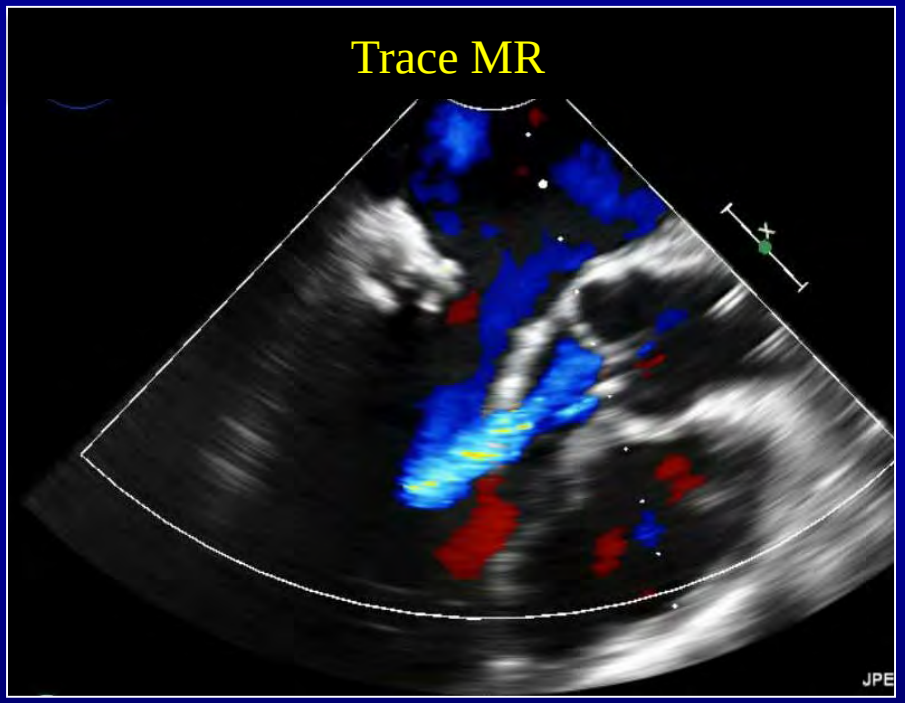


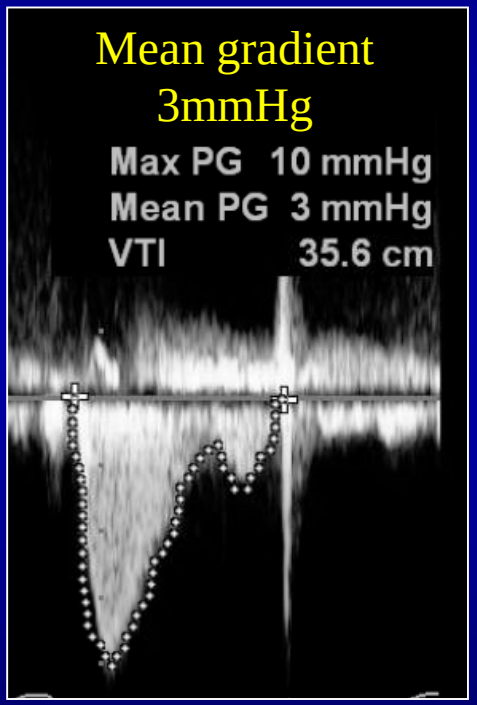
Transcatheter mitral valve replacement with a 29mm Sapien 3 valve

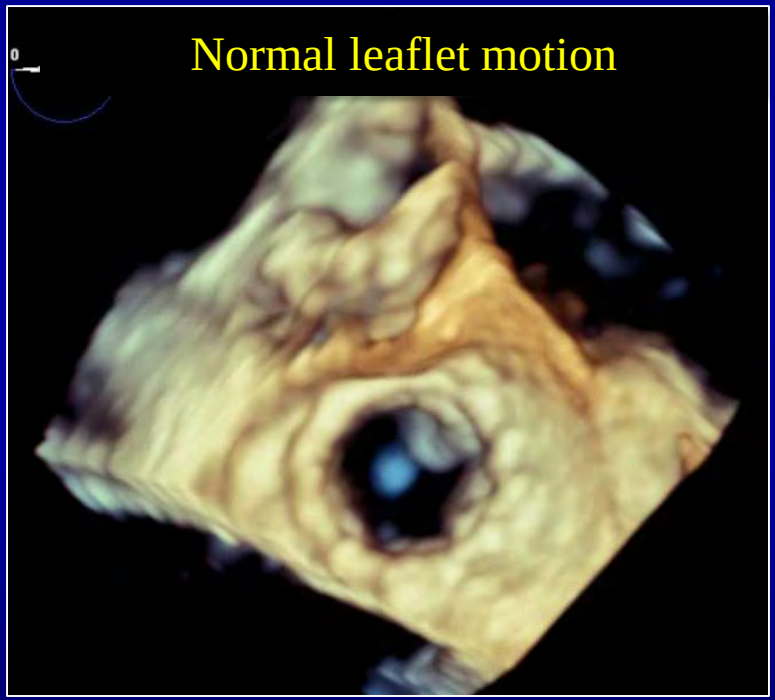
Rapid pacing at 180bpm



Final result







Frequently performed transcatheter mitral valve interventions in 2020

- MitraClip with expanding applications
- Mitral valve in valve and valve in ring
- Valve in mitral annular calcification
- Mixed valvular heart disease

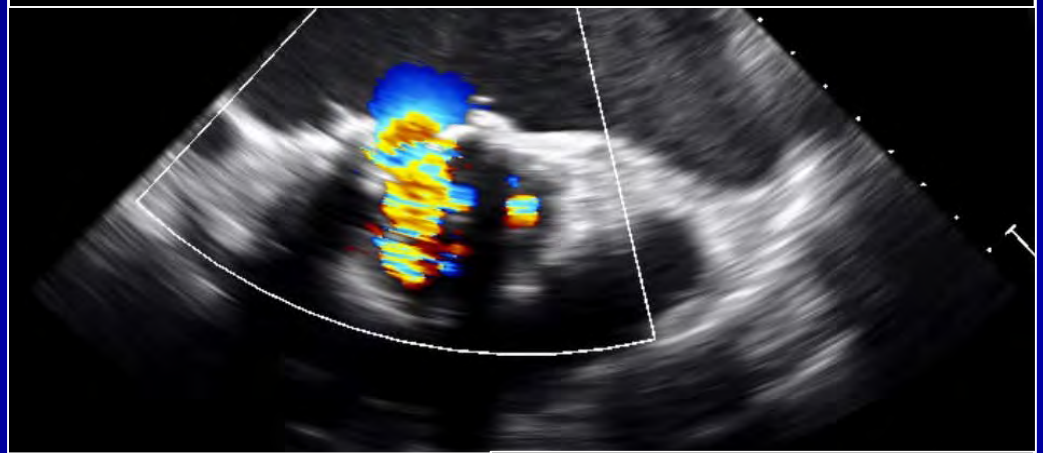
Mixed valvular heart disease

- Degenerative bioprosthetic valves
- AS plus MR
- AR plus MR
- MR plus TR

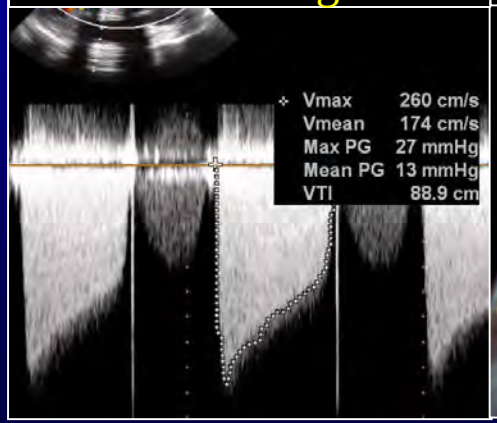
75 y/o male presenting with heart failure

Patient evaluated for transcatheter mitral ViV implantation

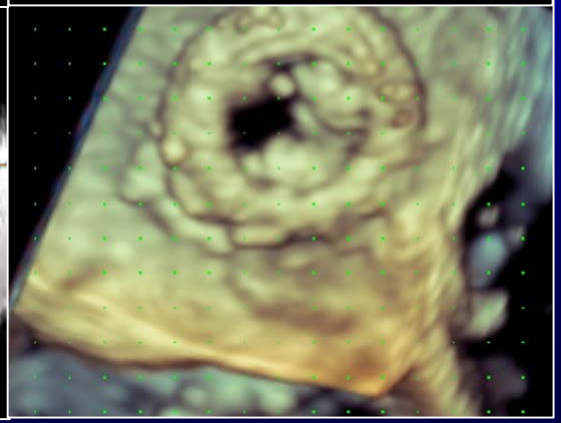
Severe mitral stenosis of #25 Magna valve



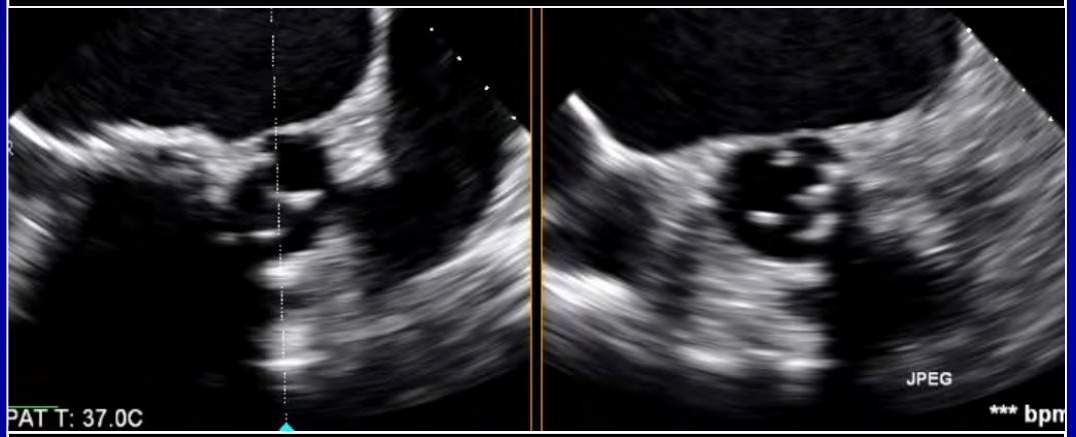
Mean mitral gradient 13mmHg



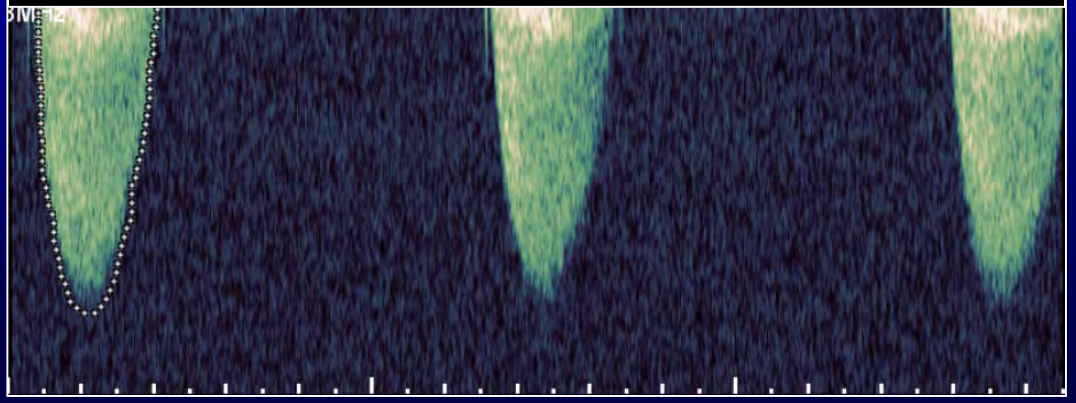
Severe restriction of mitral valve leaflets



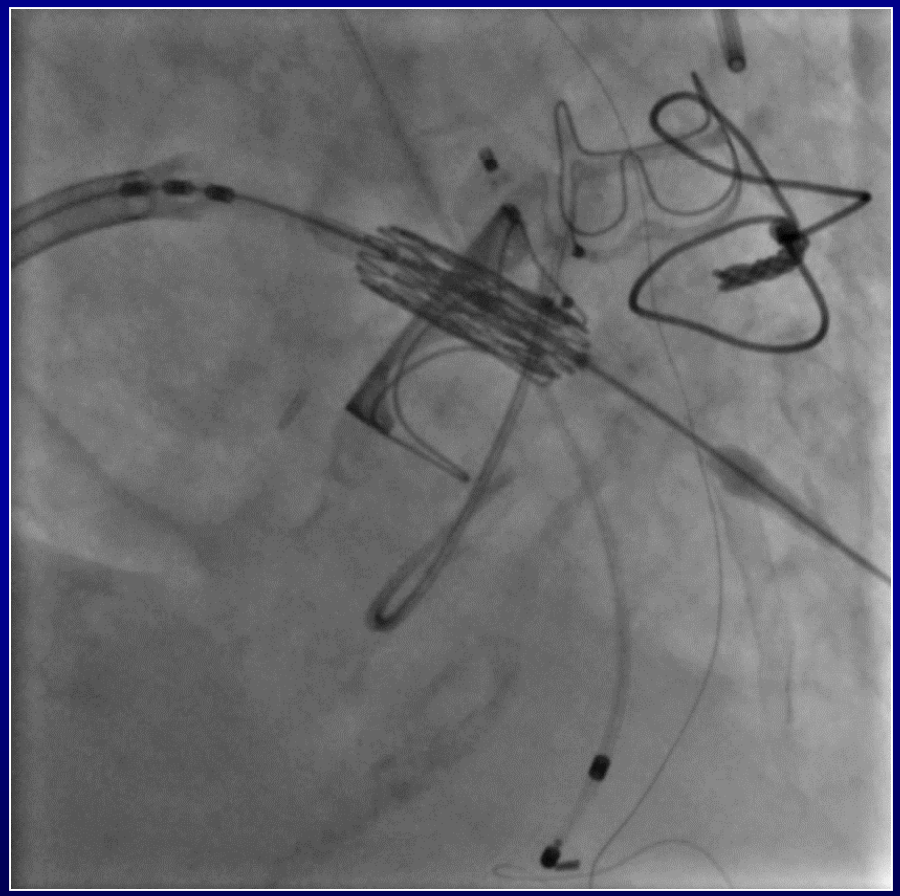
Moderate restriction of #19 Magna aortic valve and prosthesis-patient mismatch



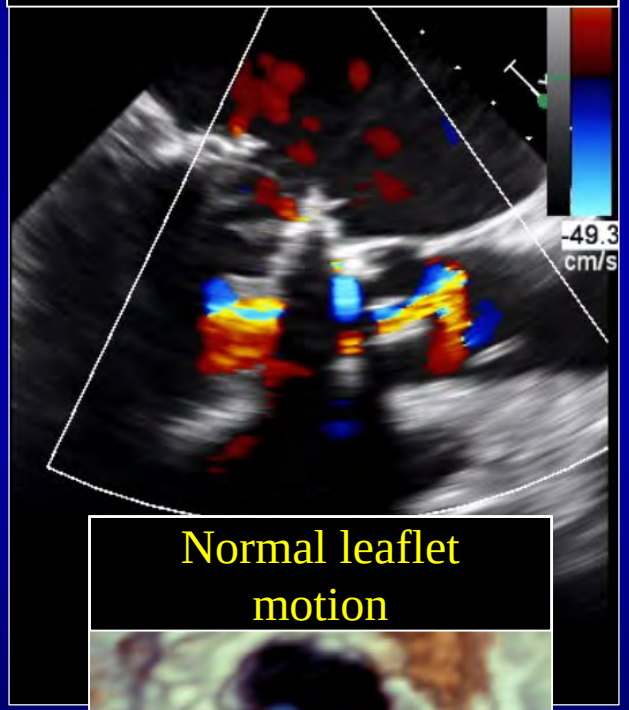
Mean aortic valve gradient 50mmHg



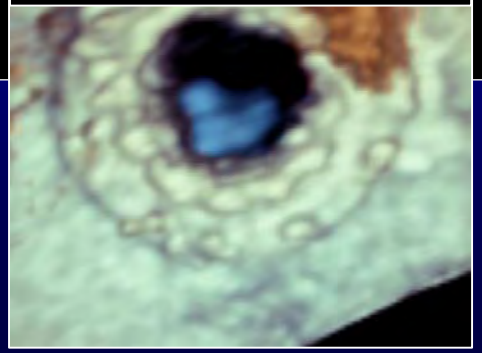
Mitral valve-in-valve performed with a 26mm Sapien 3 valve



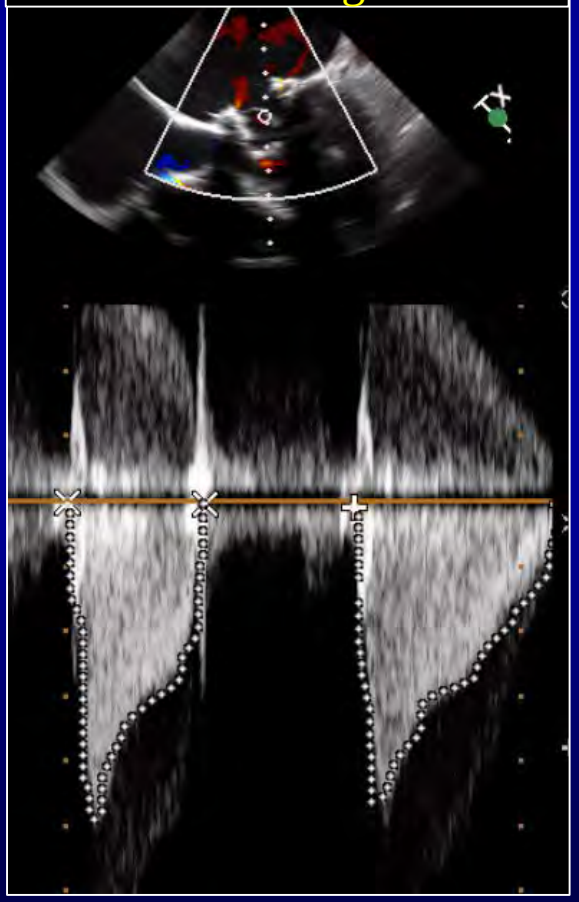
No residual MR



Normal leaflet motion

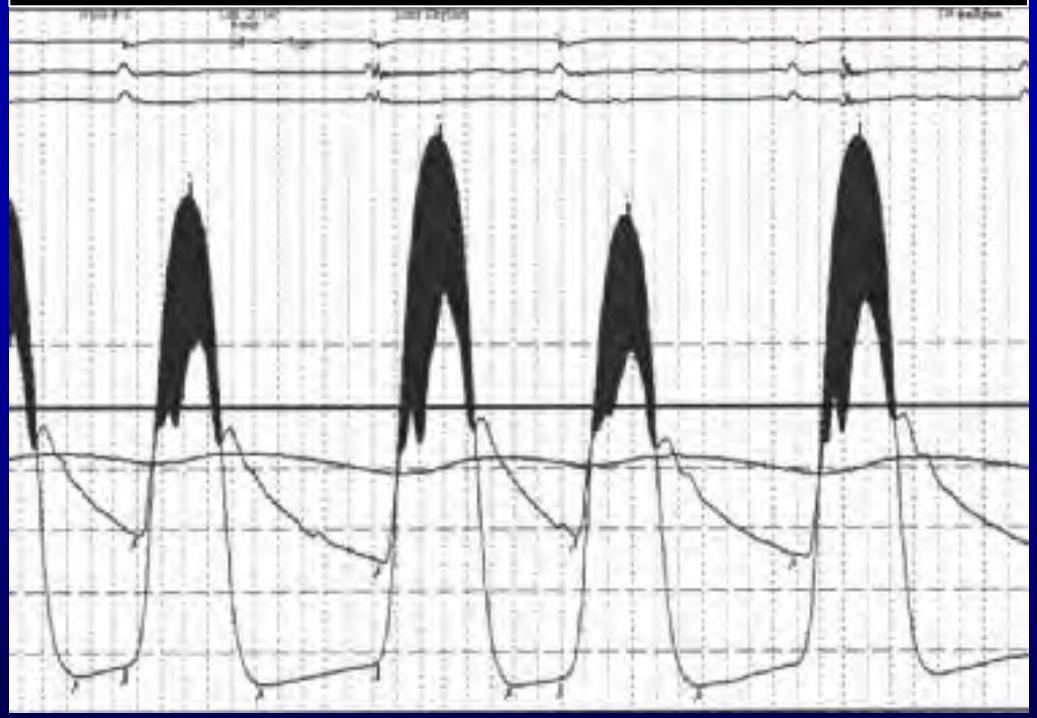


Final mitral valve gradient 4mmHg



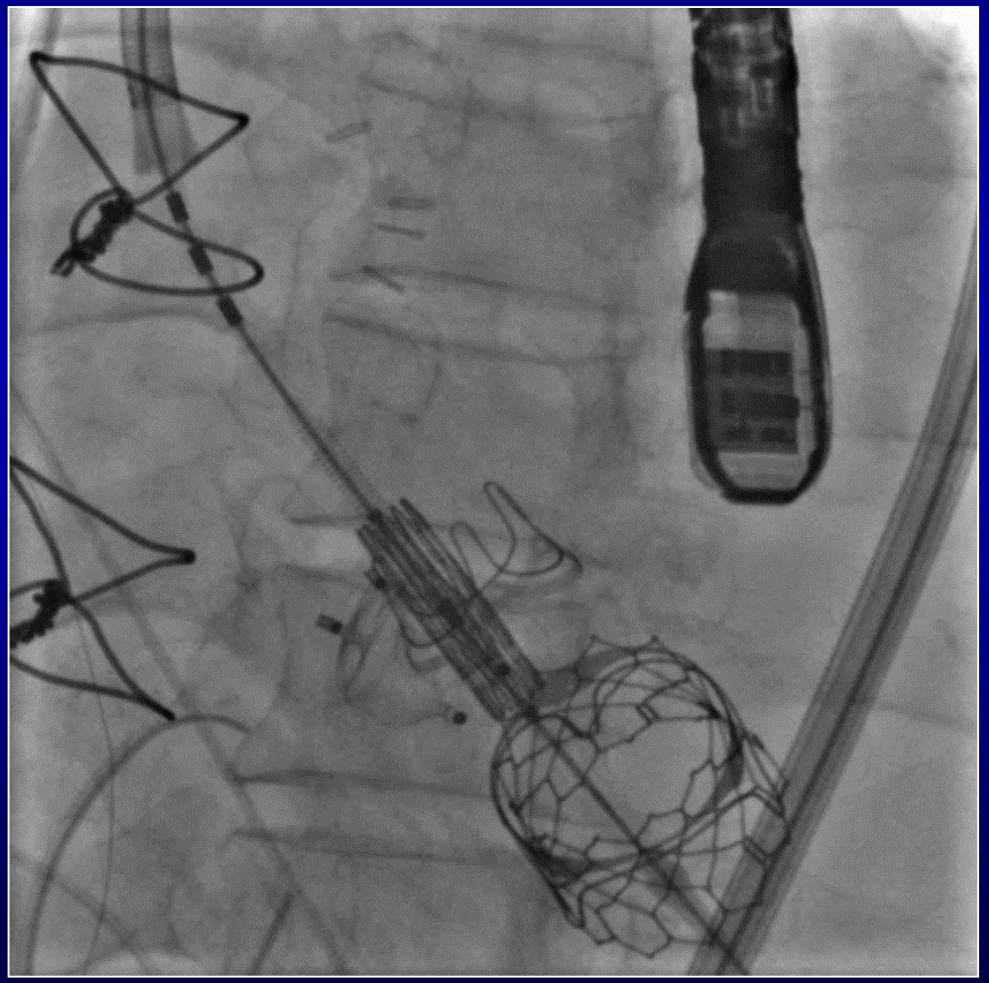
Aortic valve gradient increased following mitral valve in valve implantation

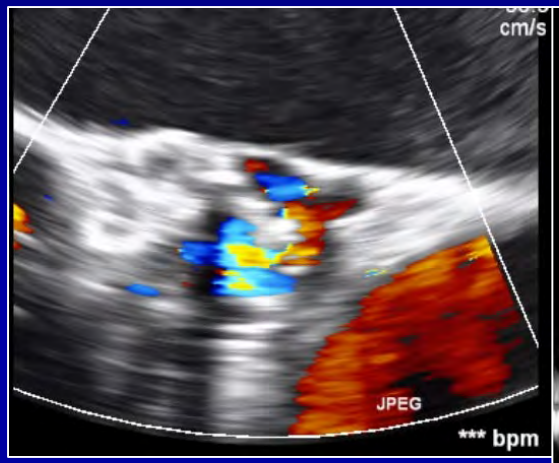
Aortic valve gradient pre-mitral
ViV: 43mmHg

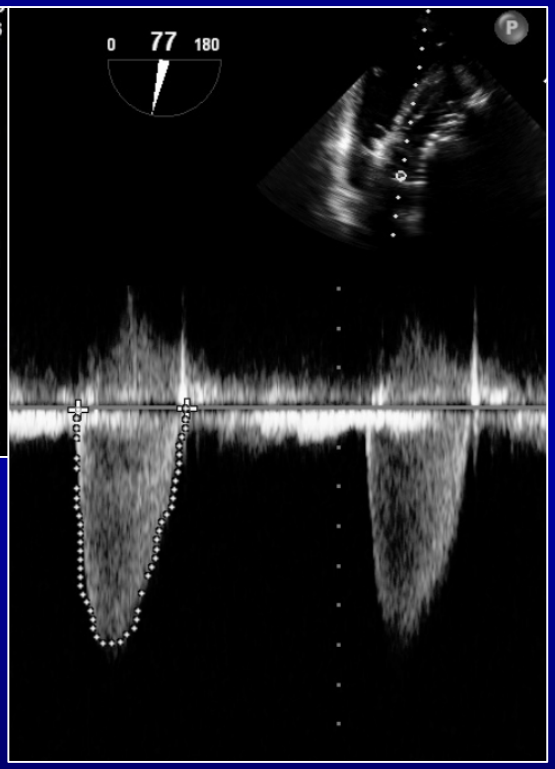


Aortic valve gradient post-mitral
ViV: 69.4mmHg

Aortic valve-in-valve performed with a 23mm Sapien 3 valve







Mixed valvular heart disease

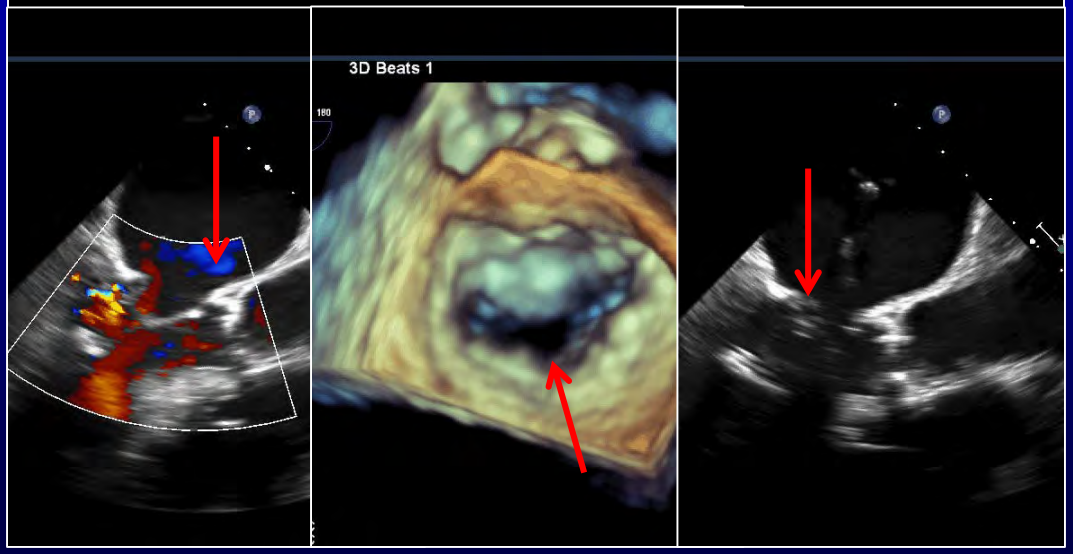
- Degenerative bioprosthetic valves
- AS plus MR
- AR plus MR
- MR plus TR

66 y/o male with severe AS and severe MR (NYHA 3-4)

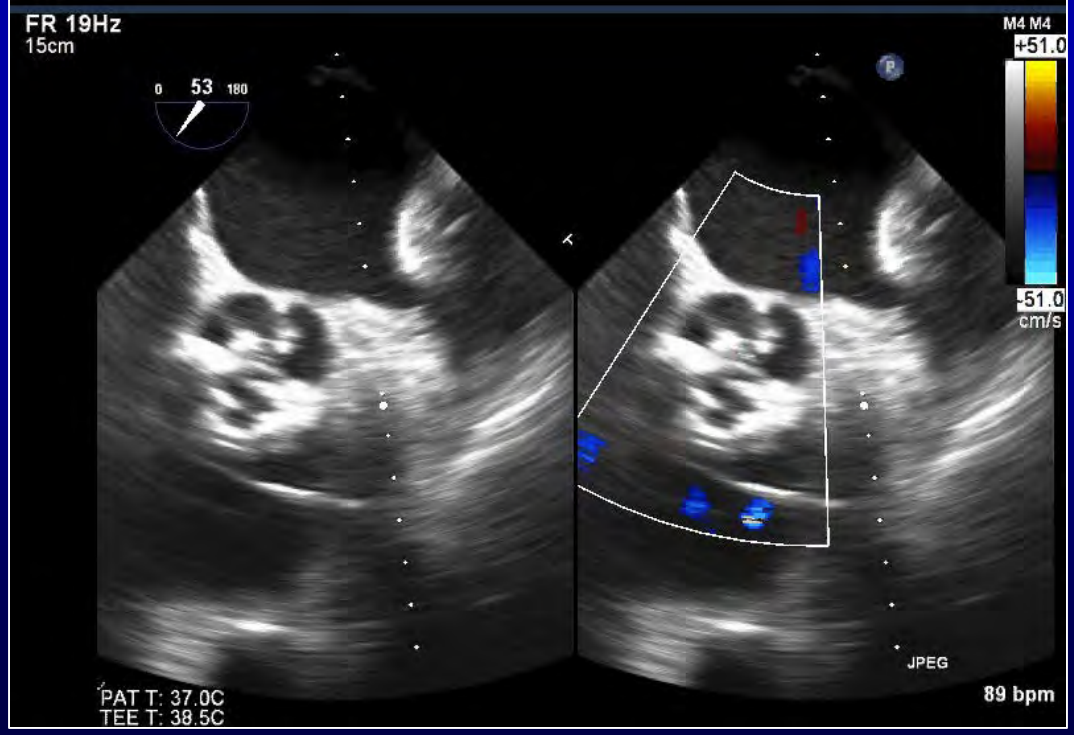
Cardiopulmonary arrest, during anesthesia induction for dual valve surgery, likely secondary to severe pulmonary hypertension (PAP 80)

Patient referred for transcatheter management of severe MR and severe AS

Severe MR with flail P2

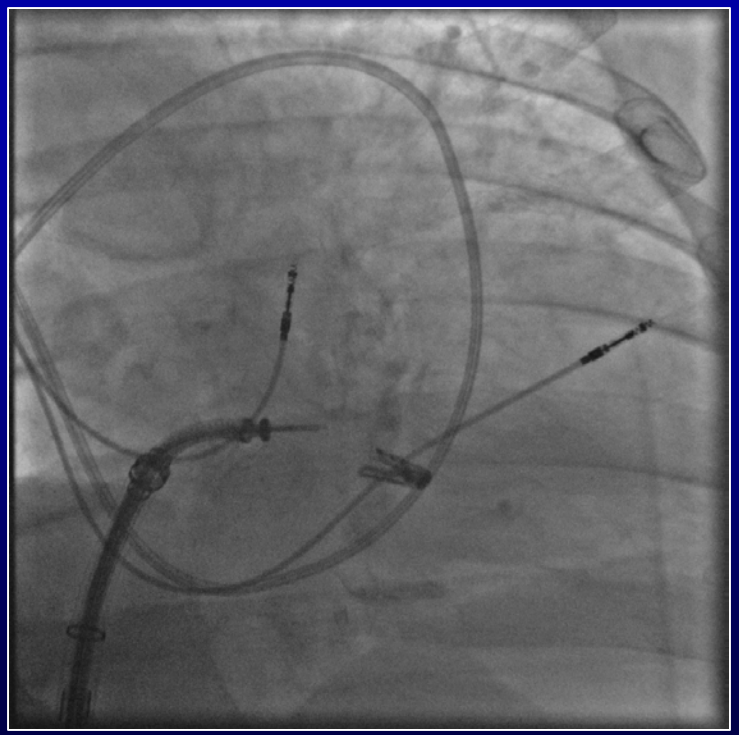


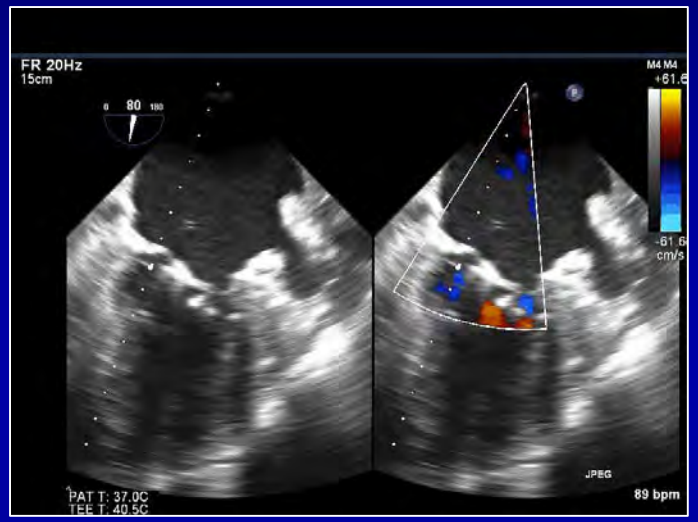
Severe AS



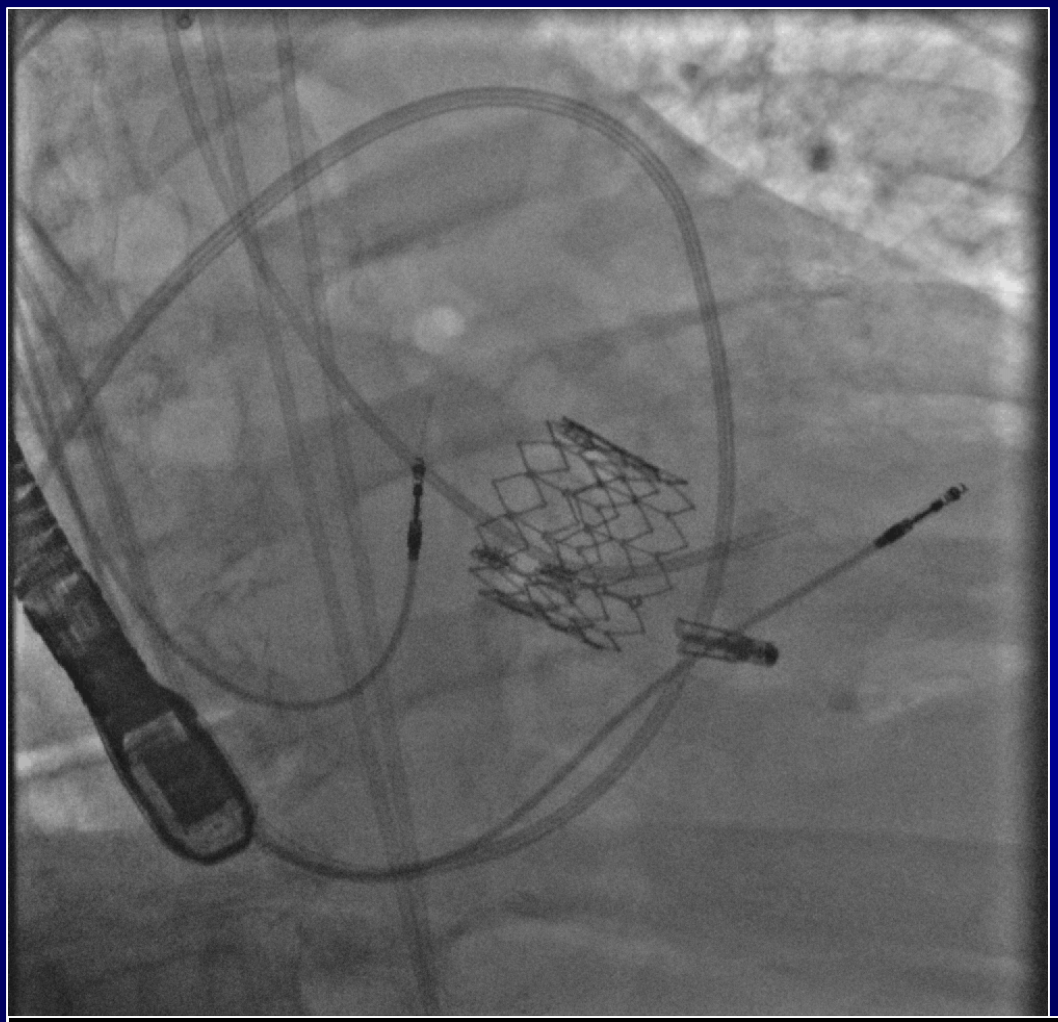
Simultaneous MitraClip and TAVR performed

MitraClip deployment with trivial residual MR

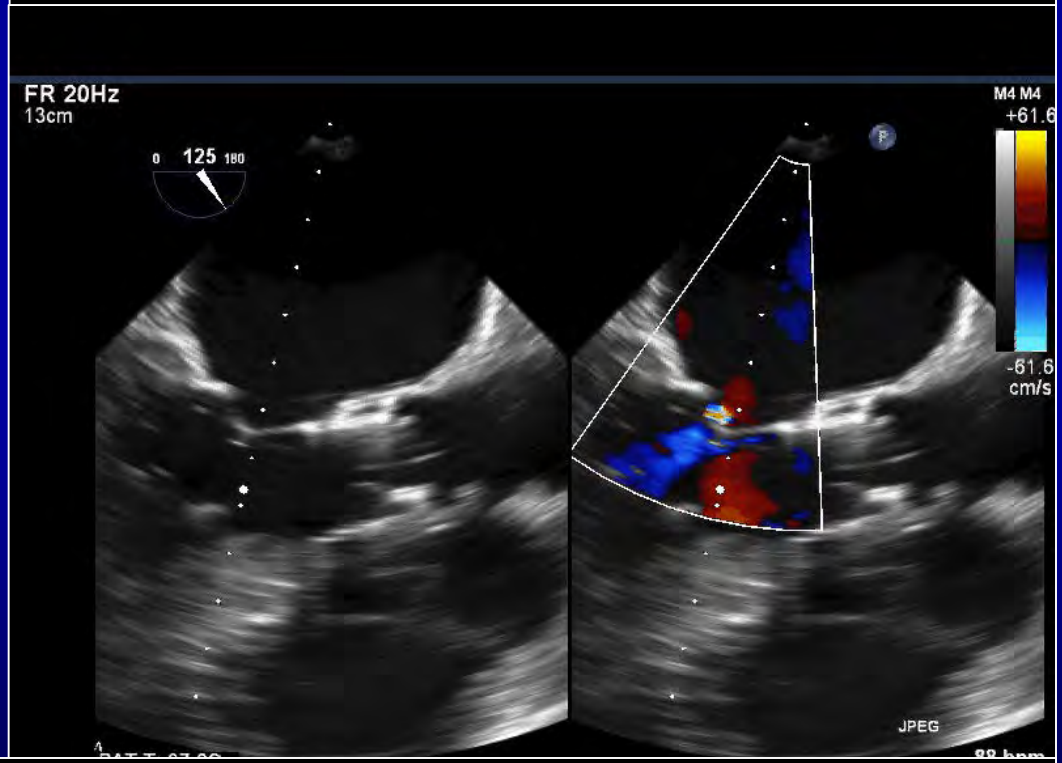




Simultaneous MitraClip and TAVR performed



29mm Sapien-XT deployment with trivial residual AR



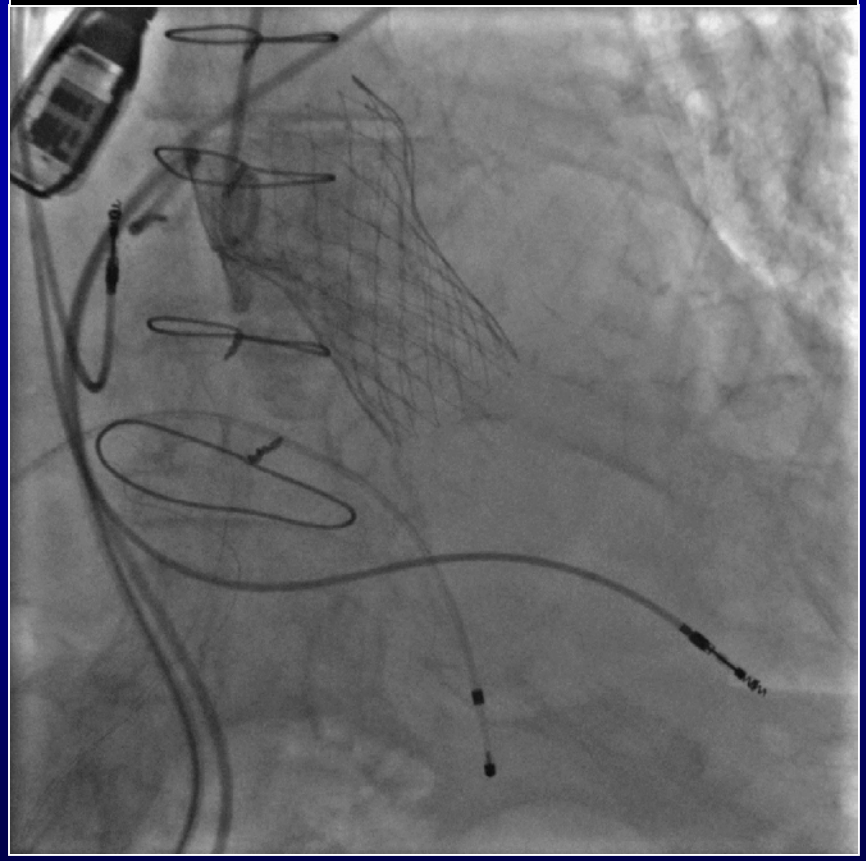
Patient discharged to home on post-procedure Day 6
NYHA Class II at 1 month

Mixed valvular heart disease

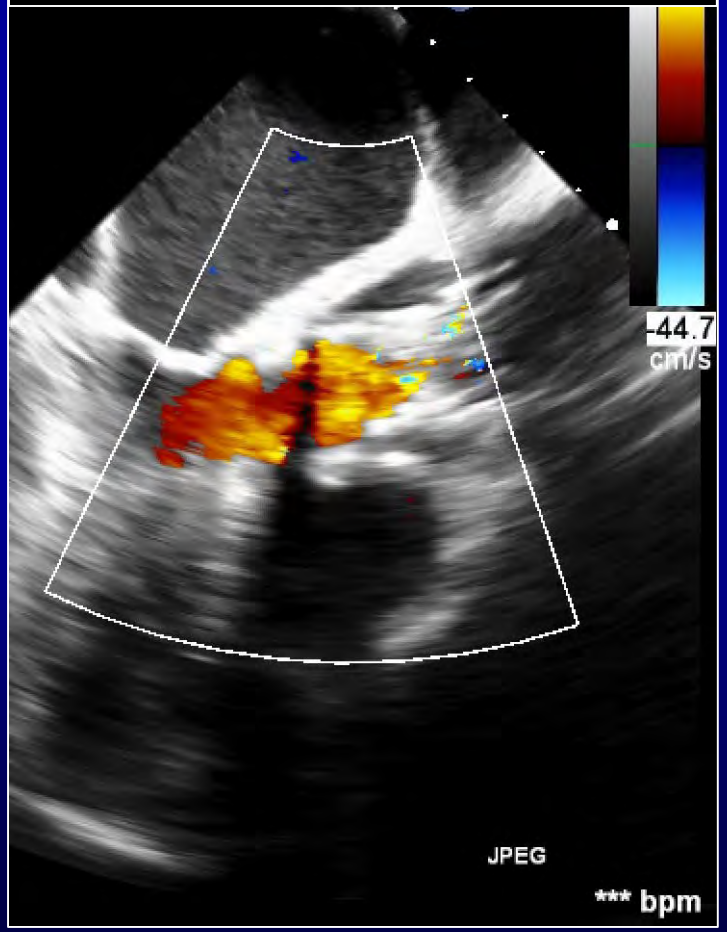
- Degenerative bioprosthetic valves
- AS plus MR
- AR plus MR
- MR plus TR

87 y/o male with severe AR due to degenerative homograft

TAVR with 29mm Evolut performed



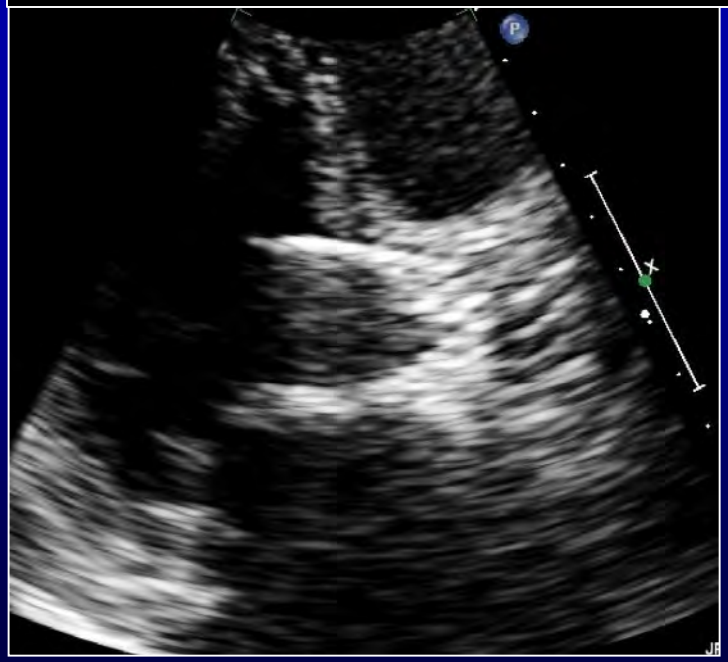
No significant AR

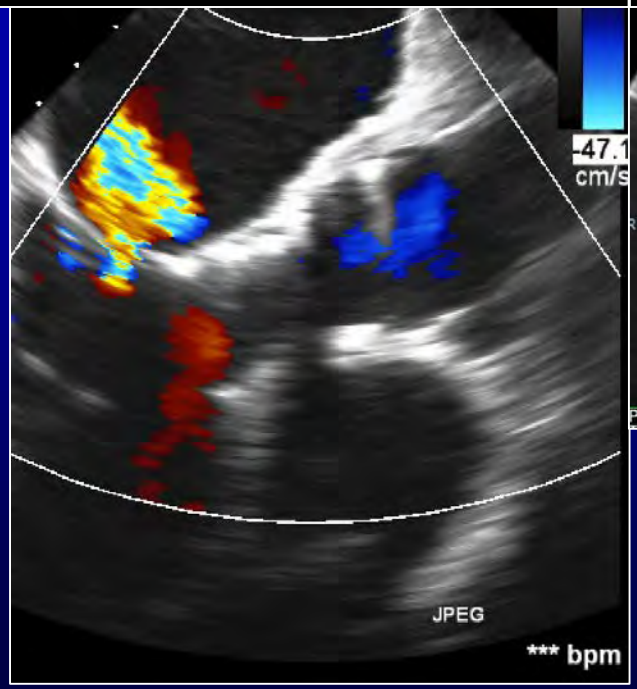


Patient presented 3 months later in decompensated heart failure and severe MR

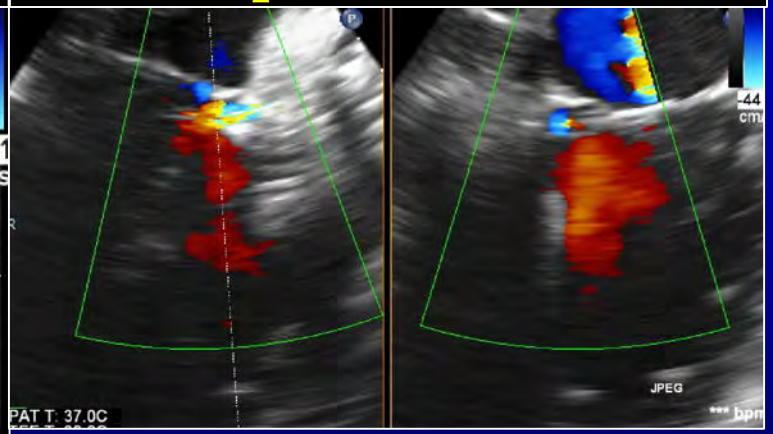
Patient brought to the cath lab for MitraClip procedure; and then the procedure was cancelled

Evolut valve impinging the mitral leaflet with severe MR



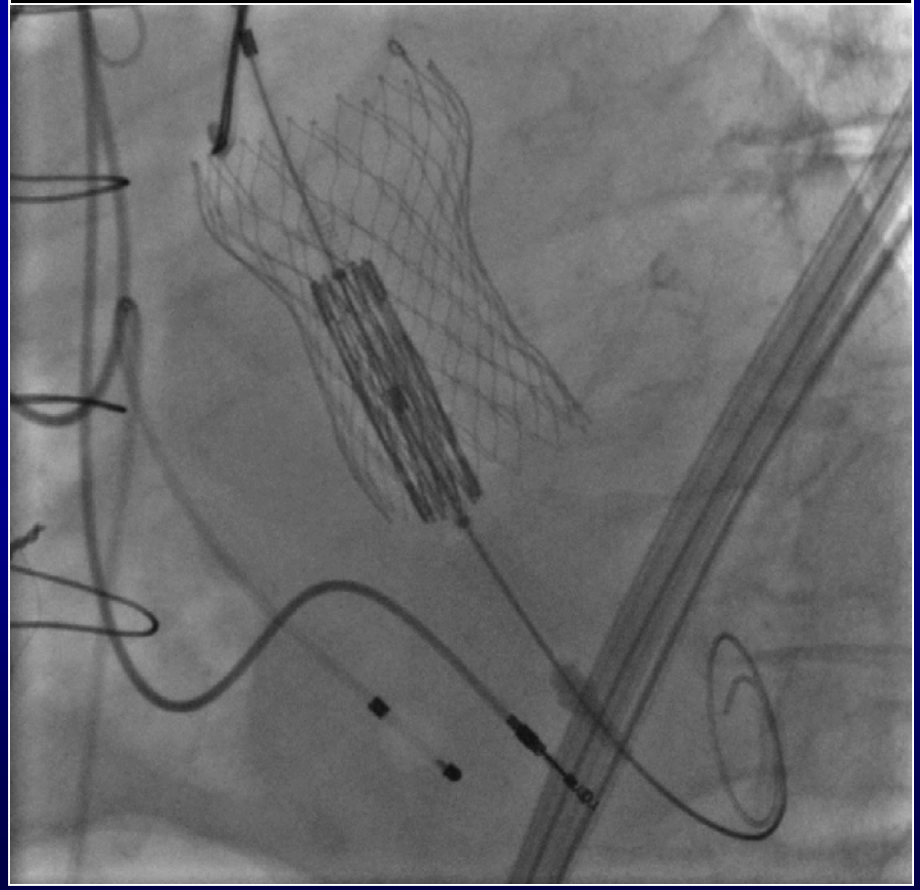


Deep Evolut valve with severe paravalvular AR

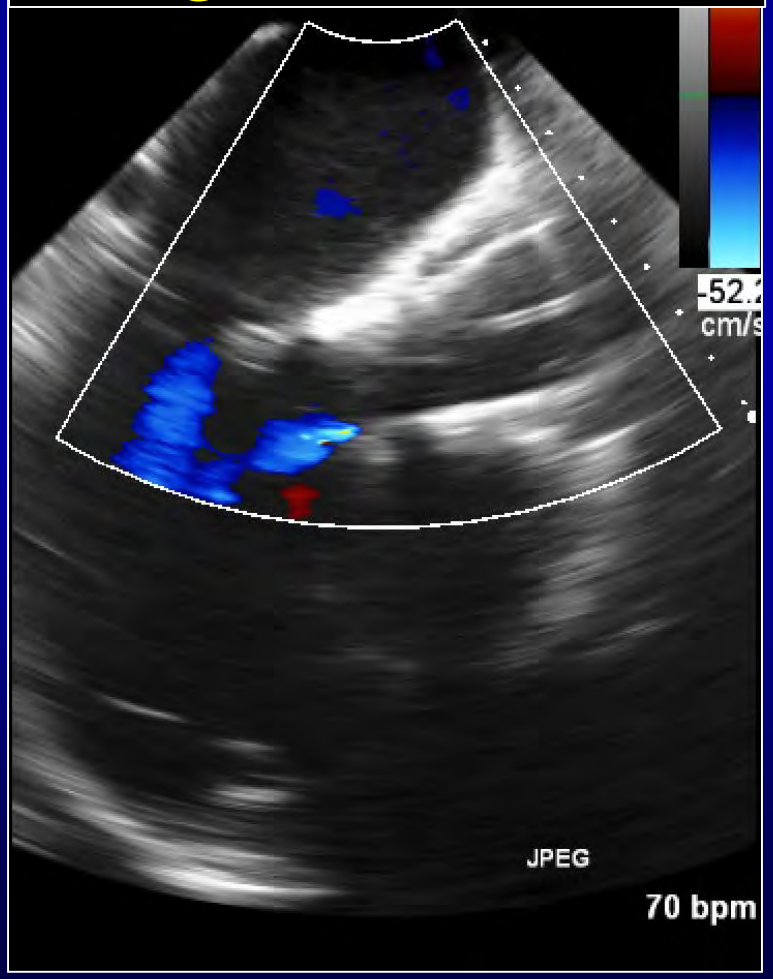


Patient brought back to the lab 3 days later for TAVR with Sapien in Evolut

Evolut valve snared into the aorta, followed by Sapien deployment



Final result
No significant AR or MR



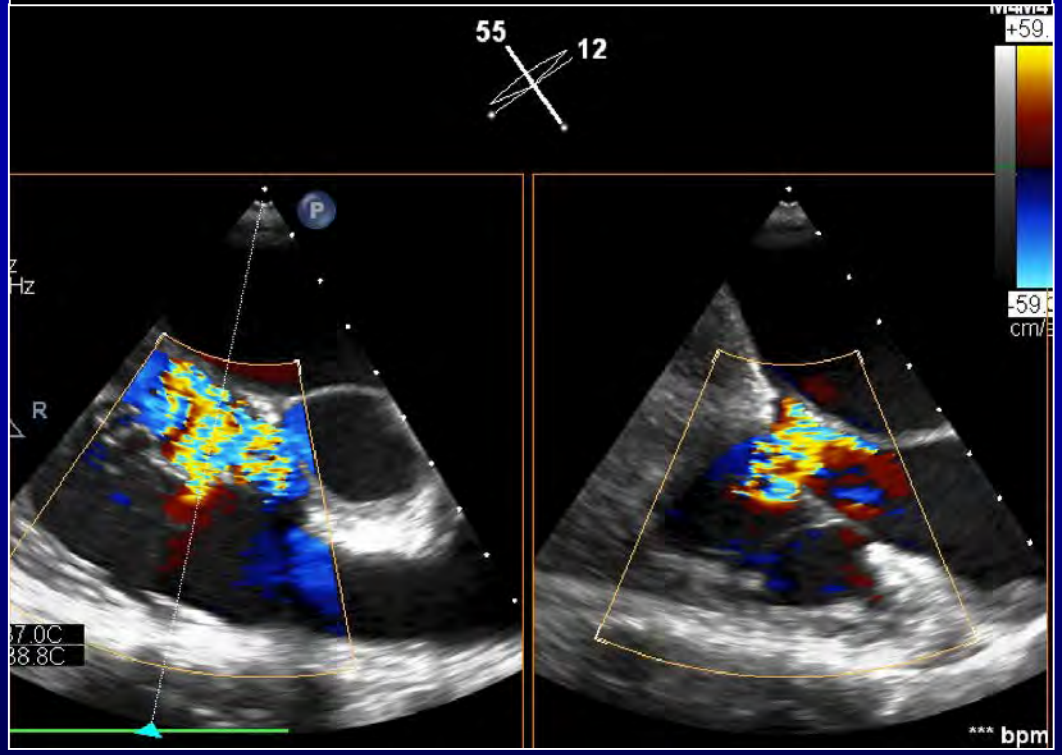
Mixed valvular heart disease

- Degenerative bioprosthetic valves
- AS plus MR
- AR plus MR
- MR plus TR

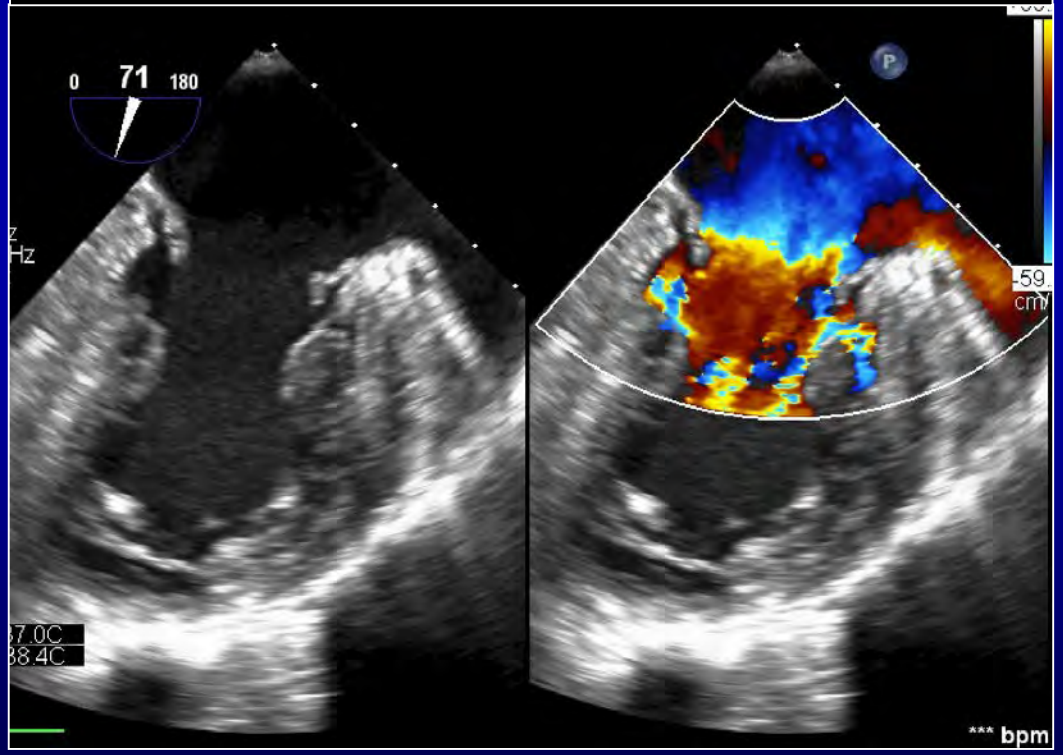
72 y/o female referred for MitraClip
Severe MR and severe TR

Patient turned down for surgery due to frailty and lack of mobility

Severe MR



Severe TR

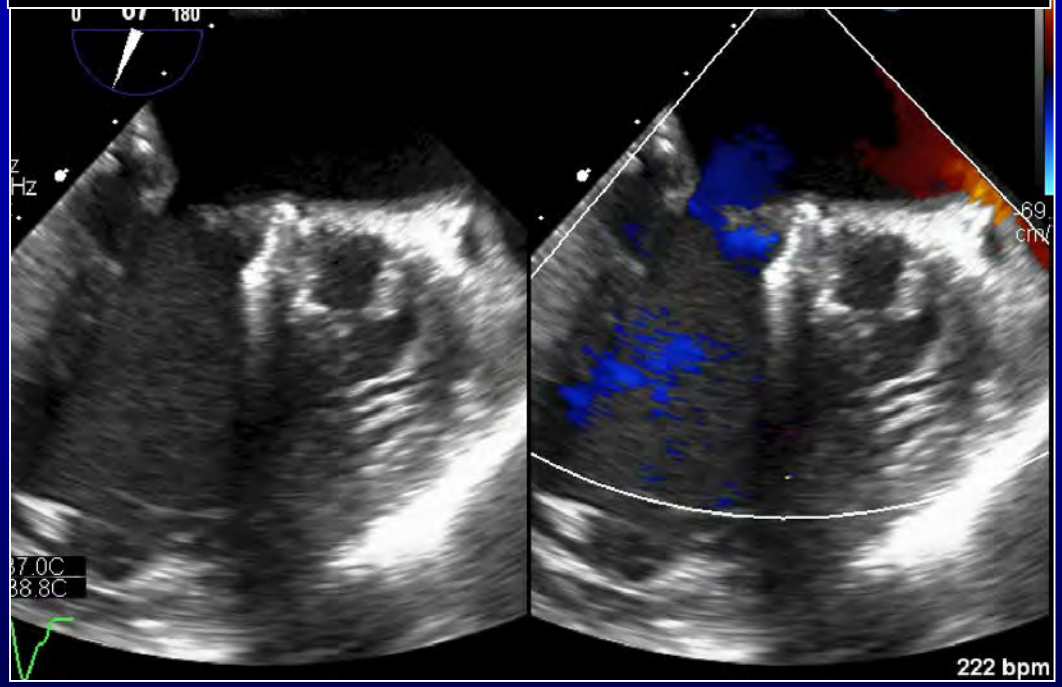


s/p 2 Mitral and 2 Tricuspid Clips
Moderate residual MR; mild TR

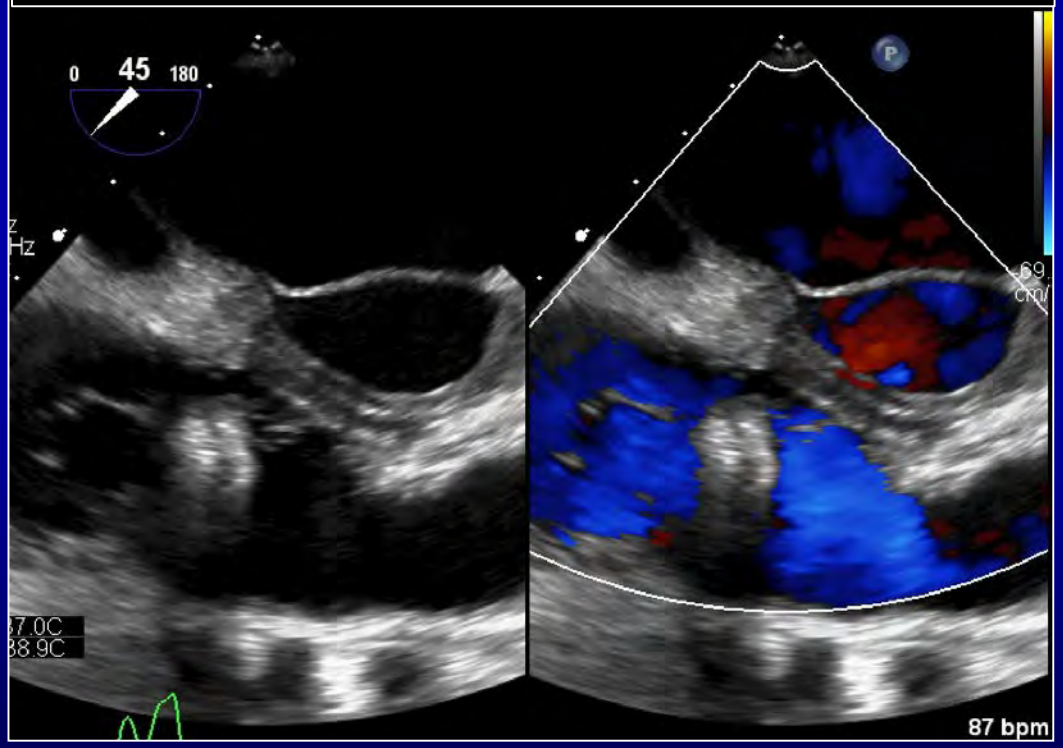
Continues to be symptomatic. Patient referred for high risk surgery

Moderate MR s/p 2 Clips

Unable to deploy additional clips due to elevated mitral valve gradient



Mild TR s/p 2 Clips

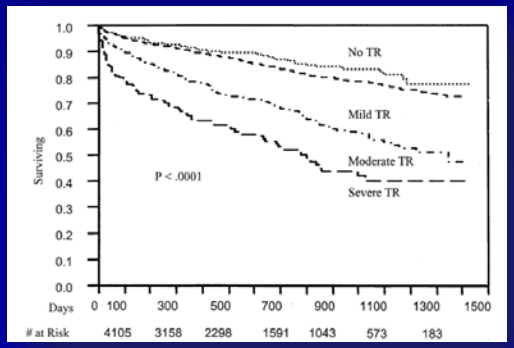


Transcatheter options for tricuspid regurgitation

Impact of tricuspid regurgitation on clinical outcomes

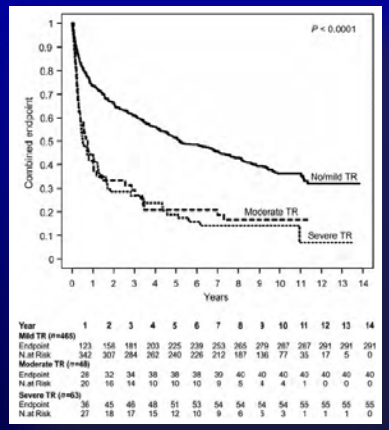
Severe and moderate TR has impact on mortality

- In MR patients
- In CHF patients
- In AS patients
- In AI patients



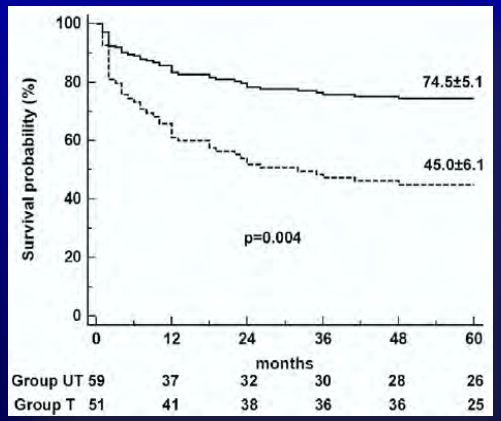
Nath et al., J Amer. Col of Cardiol., 2004

TR in CHF



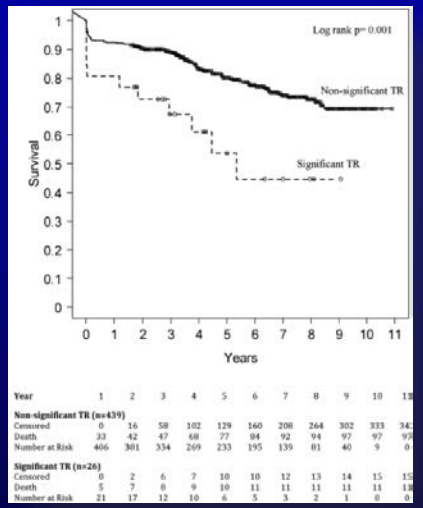
Neuhold et al, EHJ, 2013

TR in MR



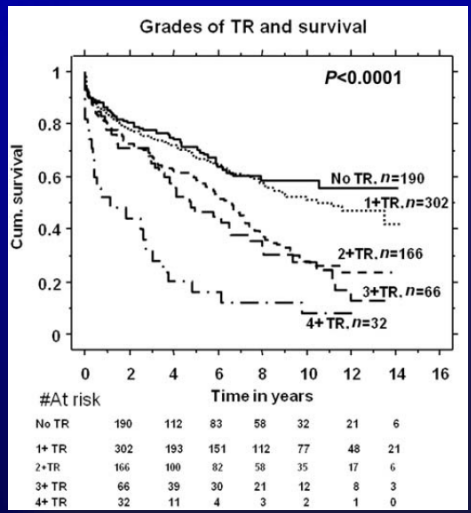
Calafiore et al, An Thor Surg, 2009

TR in Severe AS



Mascherbauer et al. , 2015

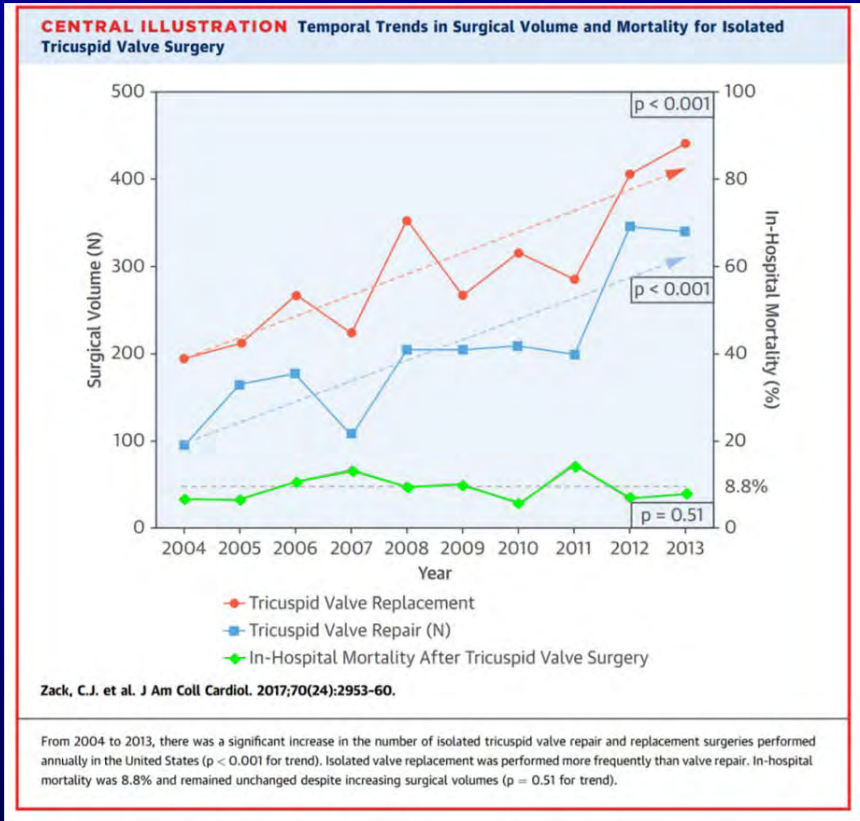
TR in Severe AI



Varadarajan, P. et al, Interactive CV and Thor Surg 2012

National Trends and Outcomes in Isolated Tricuspid Valve Surgery

Chad J. Zack, MD,[a] Erin A. Fender, MD,[a] Pranav Chandrashekar, MBBS,[a] Yogesh N.V. Reddy, MBBS,[a] Courtney E. Bennett, DO,[a,b] John M. Stulak, MD,[c] Virginia M. Miller, PhD,[c,d] Rick A. Nishimura, MD[a]



- TV replacement was performed in 59.2% of patients, whereas TV repair was performed in 40.8%.
- From 2004 to 2013, the proportion of TV replacements significantly decreased from 67.2% to 57.1% (p = 0.003).
- **In-hospital mortality = 8.8% and did not vary across the study period**

Zack CJ et al. J Am Coll Cardiol 2017;70:2953–60

Physiological and Clinical Consequences of Right Ventricular Volume Overload Reduction After Transcatheter Treatment for Tricuspid Regurgitation

- **29 patients undergoing tricuspid clip for isolated severe TR**
- **cMRI performed in 18 patients pre- and post-clip**

	Baseline (n = 18)	1 Month (n = 18)	6 Months (n = 18)	p Value	Baseline vs. 1M	Baseline vs. 6M	1M vs. 6M
Heart rate, beats/min	72.1 ± 12.8	71.8 ± 10.1	72.3 ± 11.8	0.57			
LVEF, %	52.0 ± 12.6	53.2 ± 10.7	52.4 ± 10.8	0.60	0.42	0.80	0.44
LV eccentricity index diastole ratio	1.32 ± 0.20	1.12 ± 0.09	1.14 ± 0.11	<0.01	<0.01	<0.01	0.68
LV eccentricity index systole ratio	1.04 ± 0.07	1.05 ± 0.08	1.04 ± 0.05	0.72	0.54	0.82	0.45
RV FAC, %	39.7 ± 8.8	38.7 ± 7.7	36.8 ± 8.2	0.07	0.45	0.07	0.06
TAPSE, mm	16.1 ± 4.8	15.9 ± 4.3	16.5 ± 4.5	0.68	0.82	0.68	0.38
RA area, cm^2	40.4 ± 9.1	36.1 ± 9.2	36.2 ± 9.5	<0.01	<0.01	<0.01	0.94
RA-RV pressure gradient maximum, mm Hg	38.1 ± 16.0	41.9 ± 12.8	38.9 ± 13.0	0.17	0.11	0.77	0.16
Estimated RV systolic pressure, mm Hg	49.8 ± 14.7	51.1 ± 12.2	48.1 ± 12.3	0.37	0.52	0.49	0.16
TR vena contracta, mm	9.8 ± 2.7	5.6 ± 1.5	5.7 ± 1.9	<0.01	<0.01	<0.01	0.44
TR EROA PISA, cm^2	0.6 ± 0.3	0.2 ± 0.1	0.3 ± 0.3	<0.01	<0.01	<0.01	0.20
TV regurgitant volume, ml	51.1 ± 16.5	20.6 ± 9.3	23.4 ± 7.9	<0.01	<0.01	<0.01	0.09
TV Pmean, mm Hg	1.0 ± 0.5	1.9 ± 0.5	2.1 ± 0.8	<0.01	<0.01	<0.01	0.06
TV S'-wave velocity, cm/s	9.7 ± 3.4	9.0 ± 3.2	8.8 ± 3.2	0.33	0.14	0.13	0.32
TV e'-wave velocity, cm/s	10.3 ± 3.4	9.2 ± 3.4	9.3 ± 3.5	0.33	0.13	0.19	0.81
TV E-wave velocity, cm/s	98.7 ± 35.4	117.4 ± 31.6	113.3 ± 34.6	<0.01	<0.01	<0.01	0.83
RV isovolumic acceleration, m/s^2	1.43 ± 0.48	1.39 ± 0.35	1.42 ± 0.35	0.46	0.38	0.90	0.53
RV ejection time, normalized, ms	422 ± 81	389 ± 80	374 ± 53	0.01	0.04	0.01	0.30
MV E-wave velocity, cm/s	105.4 ± 34.8	120.4 ± 40.7	117.0 ± 42.1	<0.01	<0.01	<0.01	0.18
MV e' septal velocity, cm/s	5.4 ± 1.8	5.0 ± 1.3	5.3 ± 1.2	0.40	0.25	0.55	0.36
MV e' lateral velocity, cm/s	9.4 ± 3.1	9.2 ± 2.8	9.2 ± 2.7	0.84	0.58	0.63	0.99
MV E/e' septal ratio	19.6 ± 8.6	23.3 ± 7.7	21.9 ± 8.5	0.05	0.01	0.10	0.31
MV E/e' lateral ratio	11.4 ± 5.0	13.3 ± 5.6	13.0 ± 6.3	0.01	0.01	0.03	0.69
MV E/e' mean ratio	14.3 ± 6.2	16.7 ± 6.2	16.1 ± 6.7	0.01	<0.01	0.03	0.46
Mitral regurgitation							
Grade 0	3 (10)	2 (7)	2 (7)	0.16	0.99	0.16	0.16
Grade 1	21 (72)	21 (75)	19 (68)				
Grade 2	5 (17)	5 (18)	7 (25)				
TR							
Grade 1	0 (0)	9 (32)	9 (32)	<0.01	<0.01	<0.01	0.49
Grade 2	0 (0)	18 (64)	16 (57)				
Grade 3	26 (90)	1 (4)	3 (11)				
Grade 4	3 (10)	0 (0)	0 (0)				

Consistent and sustained improvement in echocardiographic parameters after tricuspid clip

Irrespective of the baseline RV function, TAPSE, PA pressures

Rommel K-P. et al. JACC Cardiovascular Intervnetions 2019

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- **cMRI performed in 18 patients pre- and post-clip**

	Baseline (n = 18)	1M (n = 18)	6M (n = 18)	p Value	Baseline vs. 1M	Baseline vs. 6M	1M vs. 6M
Heart rate, beats/min	69.8 ± 15.8	72.0 ± 10.8	71.4 ± 9.7	0.82	0.57	0.71	0.77
LA index, ml/m²	94.8 ± 47.3	95.9 ± 44.5	95.3 ± 49.1	0.89	0.61	0.77	0.84
RA index, ml/m²	103.0 ± 41.6	99.1 ± 43.0	92.8 ± 36.9	0.38	0.60	0.17	0.35
LV mass index, g/m²	115.4 ± 34.1	116.2 ± 30.5	116.1 ± 34.8	0.90	0.69	0.73	0.96
RVEDV index, ml/m²	125.6 ± 28.9	112.4 ± 32.0	112.3 ± 33.9	<0.01	<0.01	0.01	0.98
RVESV index, ml/m²	68.5 ± 24.6	64.2 ± 25.6	65.5 ± 28.0	0.28	0.15	0.48	0.61
RVSV index, ml/m²	57.0 ± 13.4	51.4 ± 12.5	49.2 ± 12.8	0.02	0.04	0.01	0.24
RVEF, %	45.9 ± 8.7	45.8 ± 10.2	43.1 ± 8.0	0.40	0.95	0.25	0.26
RVSV effective index, ml/m²	33.4 ± 9.9	37.5 ± 9.3	36.8 ± 8.9	0.03	0.01	0.05	0.67
LVEDV index, ml/m²	79.7 ± 25.2	85.8 ± 29.5	86.0 ± 31.4	0.01	<0.01	0.01	0.88
LVESV index, ml/m²	37.0 ± 20.1	38.5 ± 20.5	40.5 ± 27.7	0.42	0.23	0.20	0.32
LVSV index, ml/m²	42.7 ± 12.0	47.3 ± 12.1	45.5 ± 10.1	0.05	0.01	0.13	0.24
LVEF, %	54.8 ± 12.3	56.4 ± 7.2	55.4 ± 10.0	0.51	0.39	0.77	0.43
LVSV effective index, ml/m²	33.4 ± 9.1	37.5 ± 9.8	36.8 ± 8.6	0.02	0.01	0.05	0.66
Aortic regurgitant fraction, %	4.1 ± 4.7	4.2 ± 4.2	3.2 ± 5.2	0.53	0.92	0.26	0.32
Pulmonary regurgitant fraction, %	2.8 ± 3.7	1.8 ± 1.6	1.0 ± 1.6	0.18	0.25	0.10	0.10
Mitral regurgitant fraction, %	18.1 ± 6.5	17.0 ± 7.6	16.2 ± 7.0	0.20	0.17	0.16	0.56
Tricuspid regurgitant fraction, %	40.7 ± 9.1	21.1 ± 5.2	21.7 ± 6.7	<0.01	<0.01	<0.01	0.73
Qp/Qs ratio	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	0.96	0.83	0.99	0.81
Cardiac index, ml/min/m²	2.2 ± 0.6	2.7 ± 0.6	2.6 ± 0.6	<0.01	<0.01	<0.01	0.52

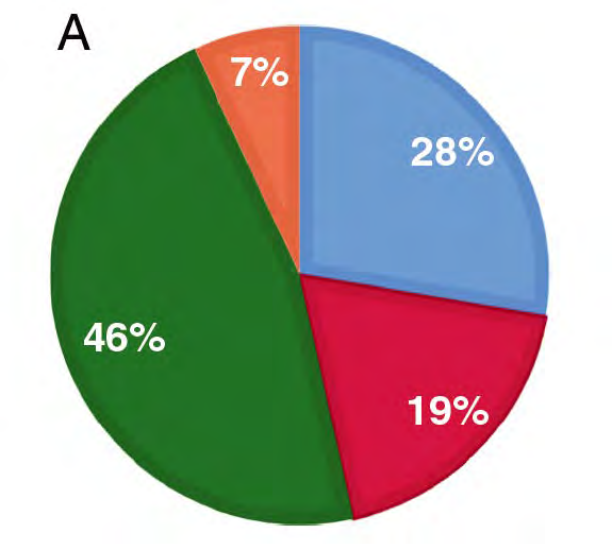
Consistent and sustained improvement in MRI parameters after tricuspid clip

Irrespective of the baseline RV function, TAPSE, PA pressures

Rommel K-P. et al. JACC Cardiovascular Intervnetions 2019

Aetiology-based clinical scenarios predict outcomes of transcatheter edge-to-edge tricuspid valve repair of functional tricuspid regurgitation

- **164 patients undergoing transcatheter tricuspid valve repair**
- **Procedural success defined as >1 grade reduction in TR**



Clinical Scenarios	Group Definitions
Dialysis-CS	Chronic haemodialysis
MR-CS	MR ≥grade 3; no haemodialysis
PAPs-CS	Invasive PAPs ≥50 mmHg; MR <grade 3; no haemodialysis
Afib-CS	History of atrial fibrillation/flutter; invasive PAPs <50 mmHg; MR <grade 3; no haemodialysis

Schlotter F. et al. European Journal of Heart Failure 2019

Aetiology-based clinical scenarios predict outcomes of transcatheter edge-to-edge tricuspid valve repair of functional tricuspid regurgitation

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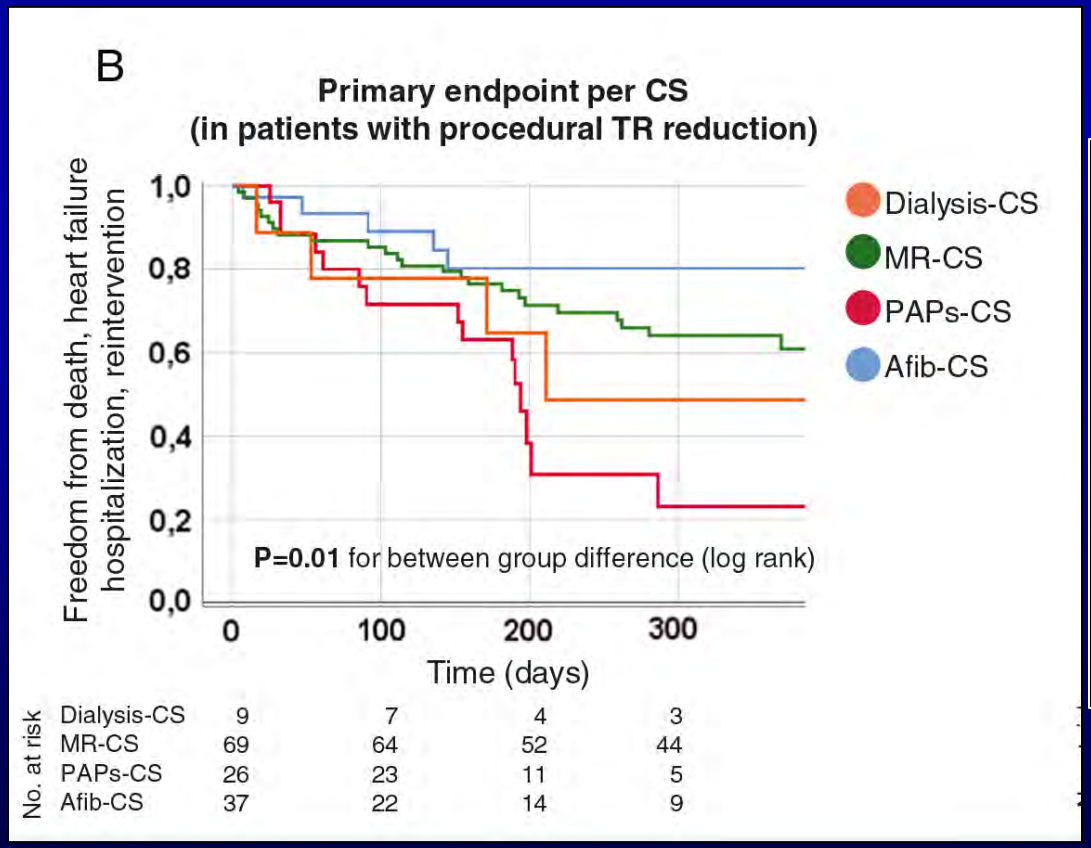

Patients with pulmonary hypertension (Invasive sPAP > 50mmHg) had worse outcomes

Freedom from death, heart failure hospitalization or reintervention

Schlotter F. et al. European Journal of Heart Failure 2019

Aetiology-based clinical scenarios predict outcomes of transcatheter edge-to-edge tricuspid valve repair of functional tricuspid regurgitation

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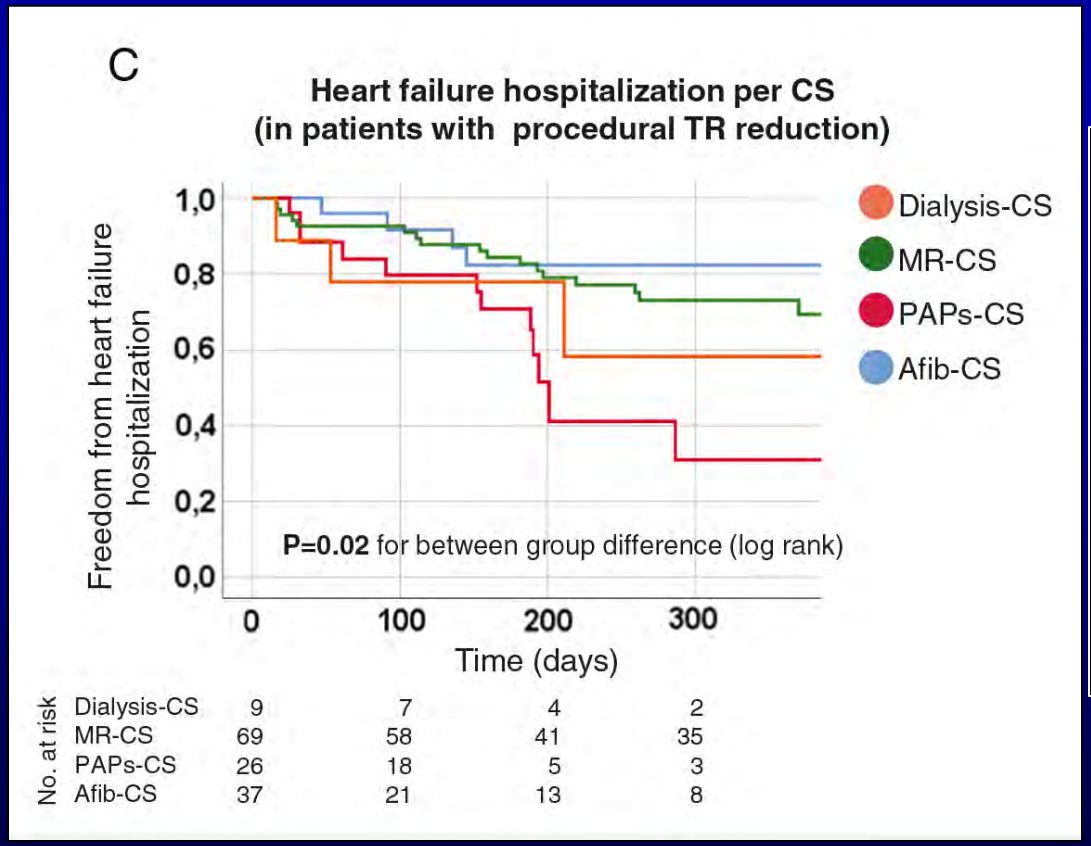


Patients with pulmonary hypertension (Invasive sPAP > 50mmHg) had worse outcomes

Freedom from heart failure hospitalization

Schlotter F. et al. European Journal of Heart Failure 2019

Impact of Severe Tricuspid Regurgitation on Accuracy of Echocardiographic Pulmonary Artery Systolic Pressure Estimation

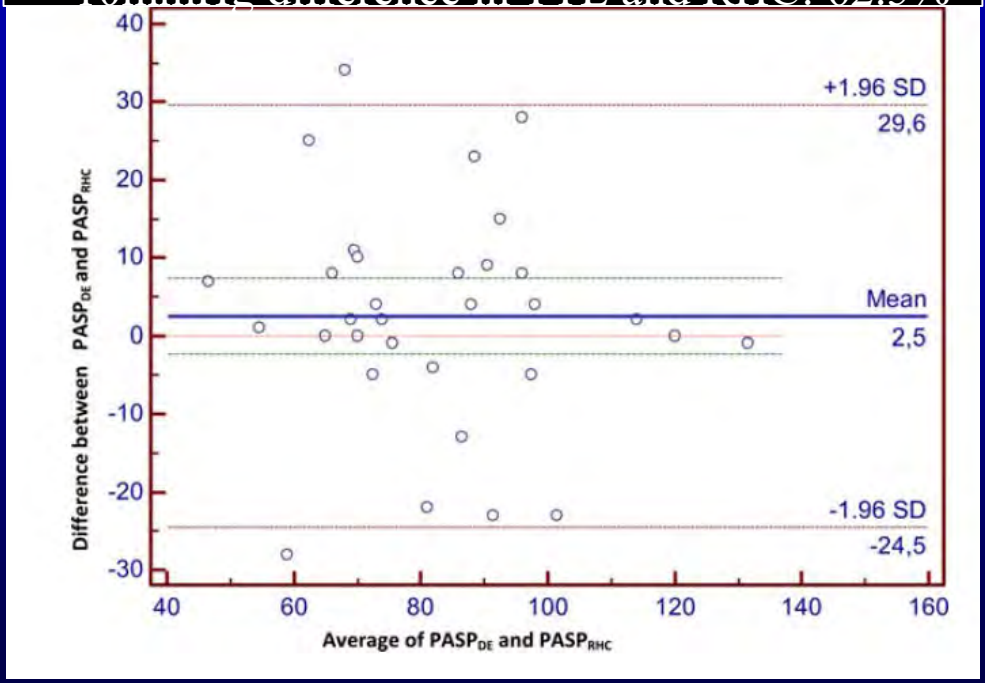
- 36 patients with mild-moderate TR
- 36 patients with severe TR

In patients with PAH, the presence of severe TR is associated with an overestimated PASP measurement on echocardiography

Mild-moderate TR

Difference between TTE and RHC: 2.5mmHg

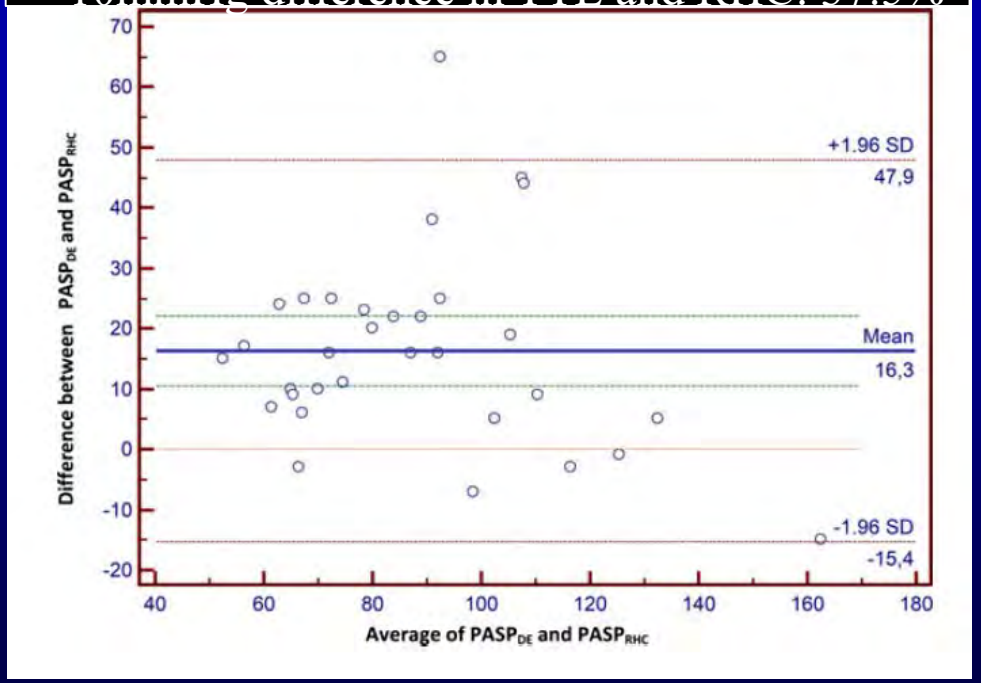
< 10mmHg difference in TTE and RHC: 62.5%



Severe TR

Difference between TTE and RHC: 16.3mmHg

< 10mmHg difference in TTE and RHC: 37.5%



Ozpelit E. et al. Echocardiography 2015

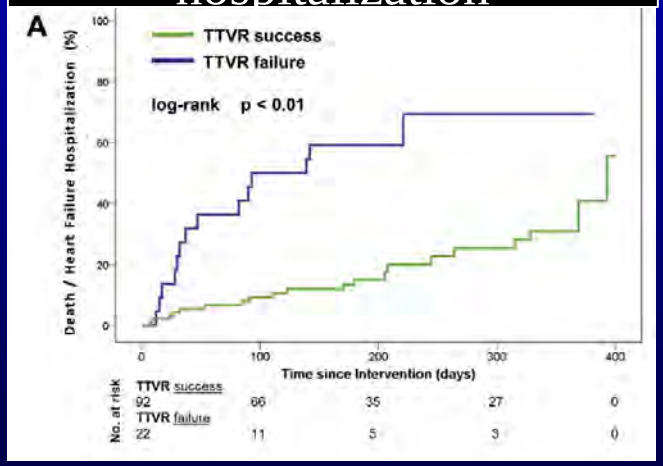
Predictors of Procedural and Clinical Outcomes in Patients With Symptomatic Tricuspid Regurgitation Undergoing Transcatheter Edge-to-Edge Repair

- **117 patients undergoing transcatheter tricuspid valve repair with MitraClip**
- **Procedural success defined as >1 grade reduction in TR**

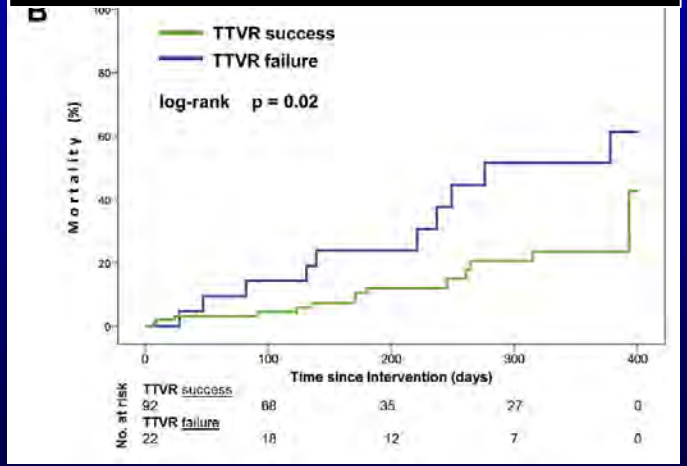
Successful tricuspid valve repair associated with improved survival and heart failure hospitalization

Procedural success of tricuspid valve repair was the only predictor of clinical outcomes (HR 0.20, 95% CI 0.08-0.48)

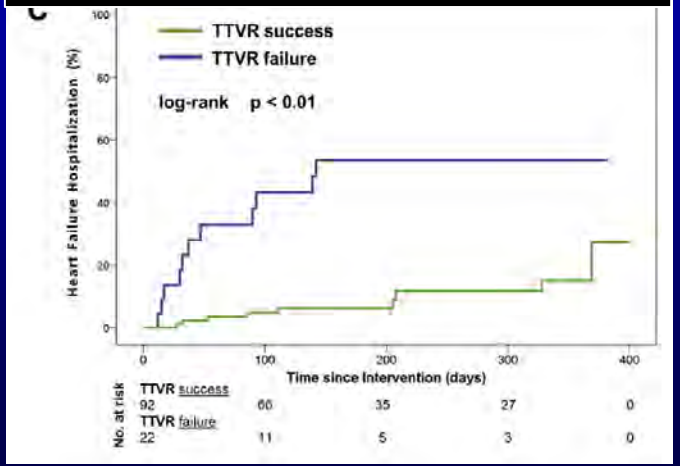
Death/heart failure hospitalization



Death



Heart failure hospitalization

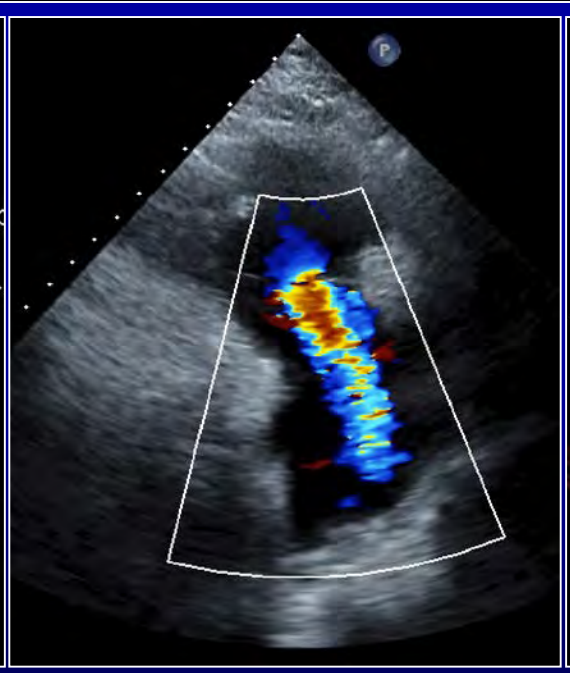


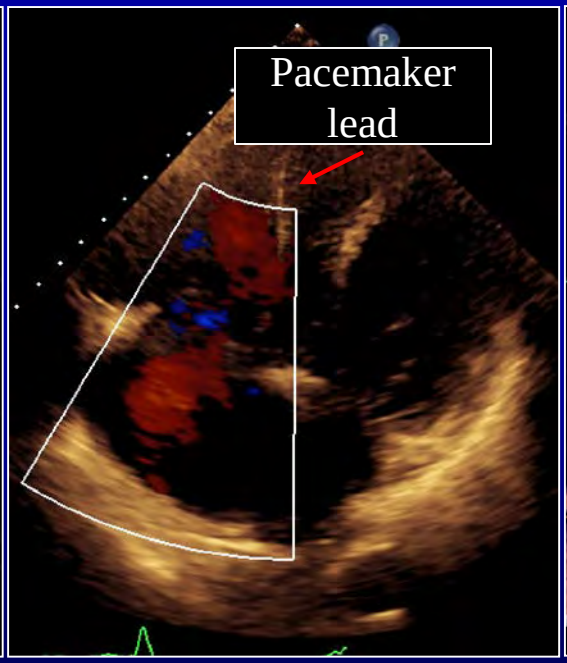
Besler C. et al. JACC: Cardiovascular Interventions 2018

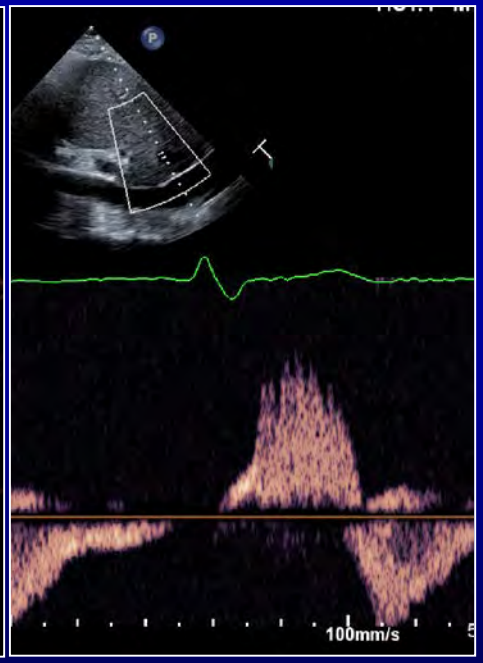
74 y/o male with NYHA ambulatory 4 heart failure >5 hospitalizations in 3 months

Severe tricuspid regurgitation with moderately dilated RV
Normal LV function

Hepatic vein flow
Systolic flow reversal



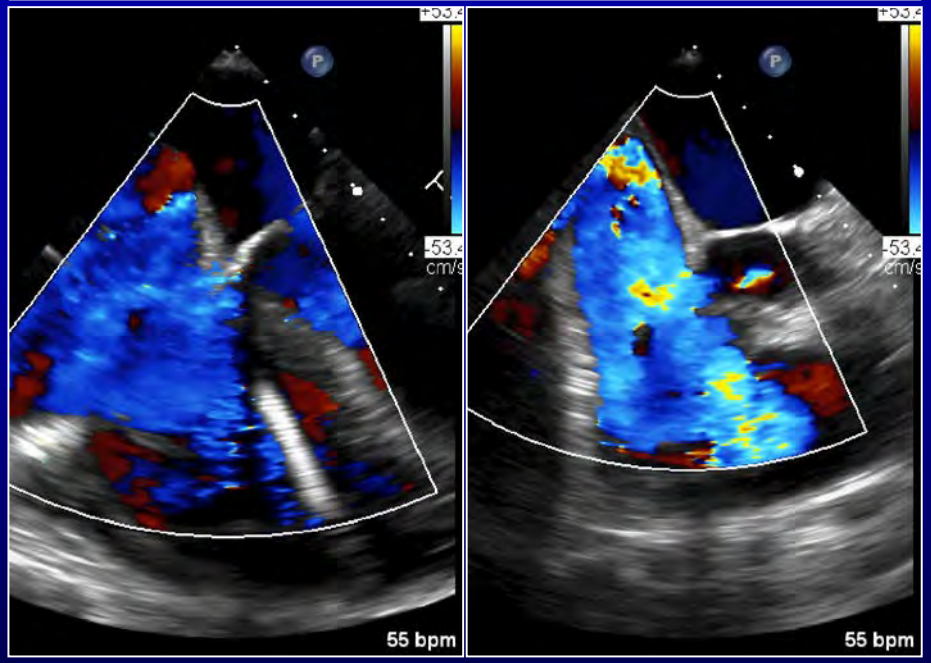




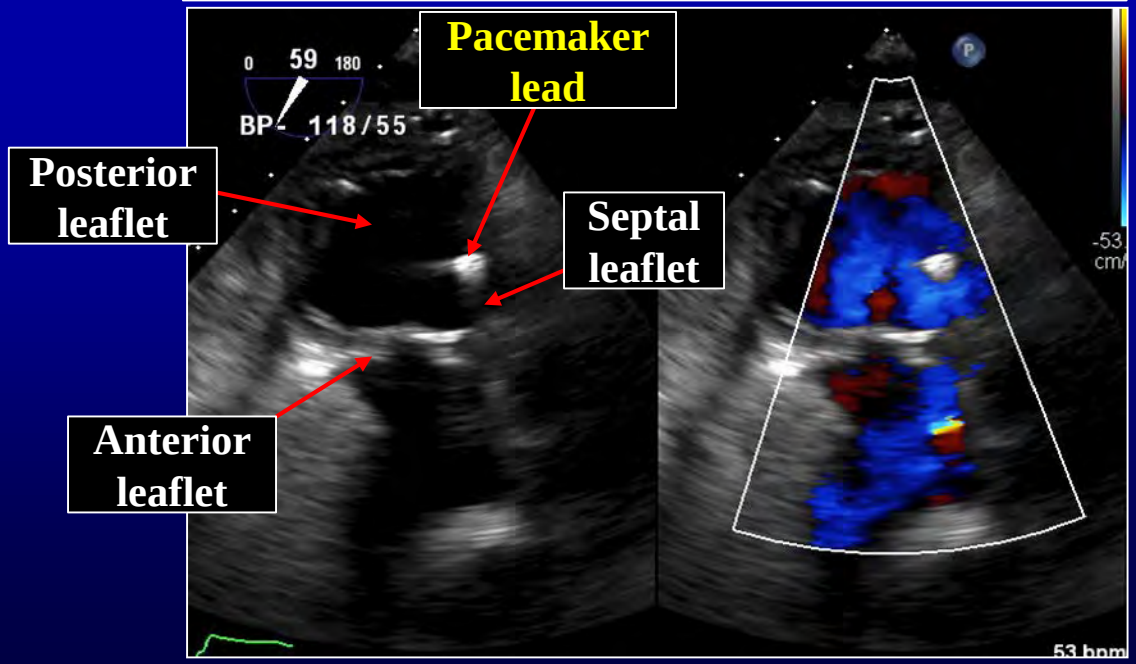
Patient consulted for tricuspid clip
TEE obtained for pre-procedural evaluation

Technically challenging for tricuspid clip due to the wide coaptation gapt secondary to leaflet restriction by the pacemaker lead

Severe tricuspid regurgitation



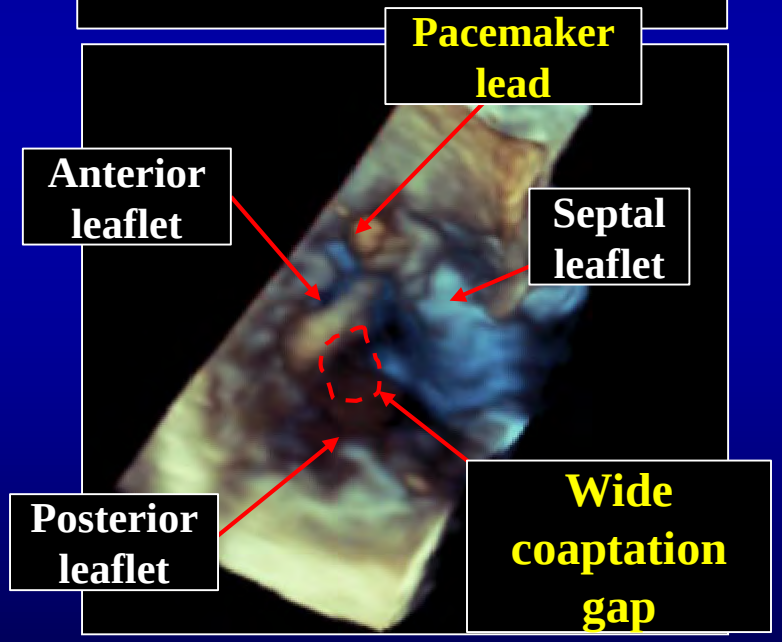
Significant restriction of the septal leaflet due to pacemaker lead



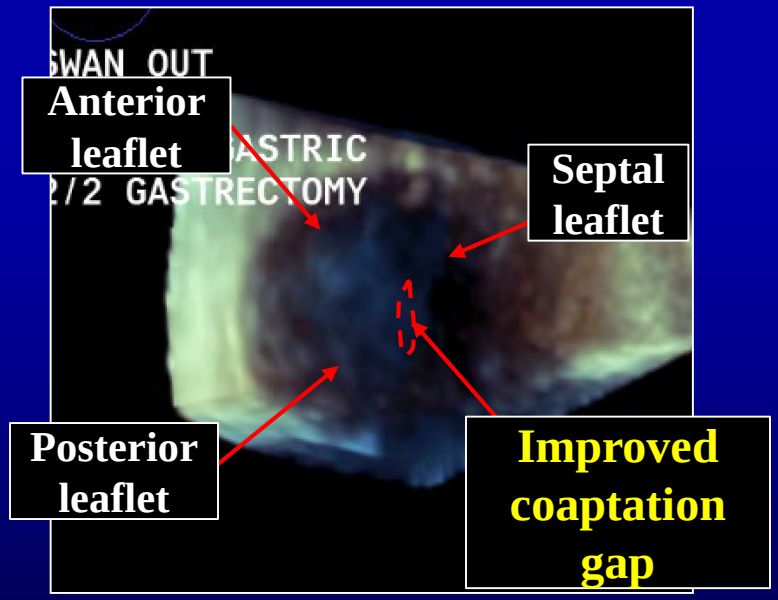
Patient sent for surgical pacemaker lead removal
No pacing required in the last 2 years

No change in the severity of TR after removal of the pacemaker lead

Before lead removal



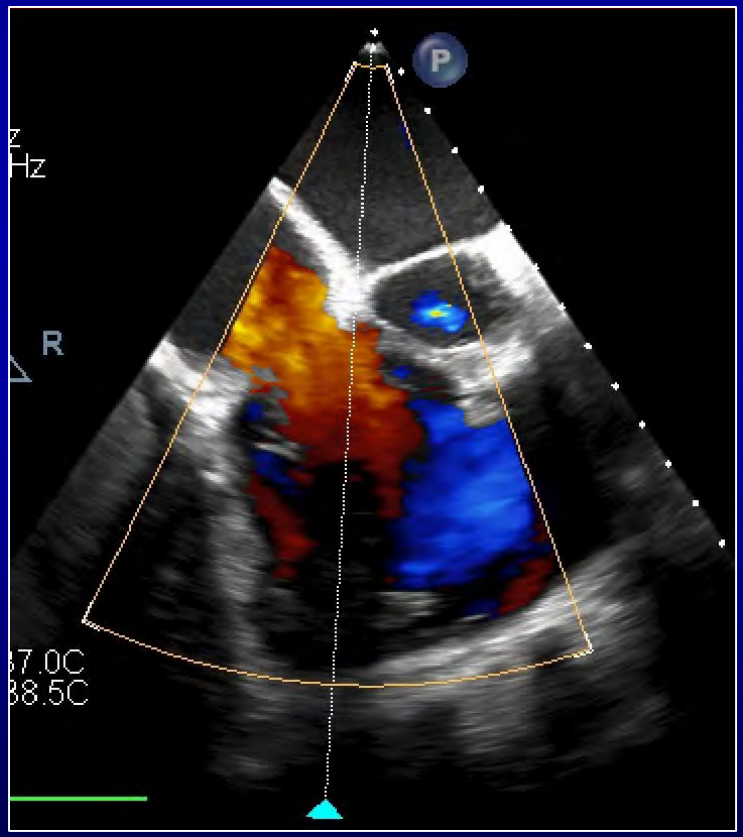
After lead removal



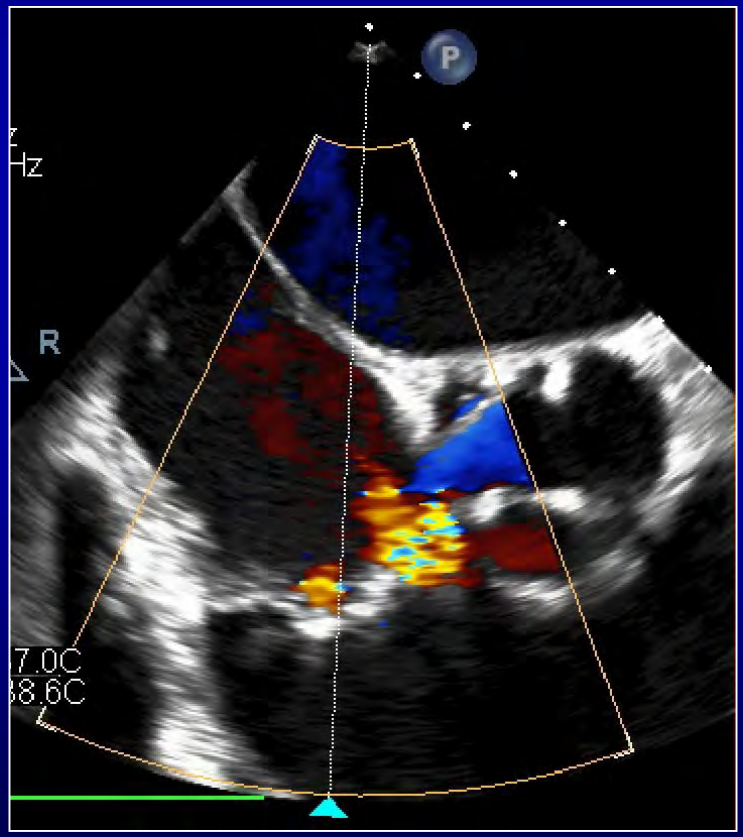
Patient readmitted 1 week later for heart failure
Brought to the cath lab for tricuspid clip

s/p 3 Clips

Baseline
Torrential TR



s/p 3 clips
Mild TR



Patient readmitted 1 week later for heart failure
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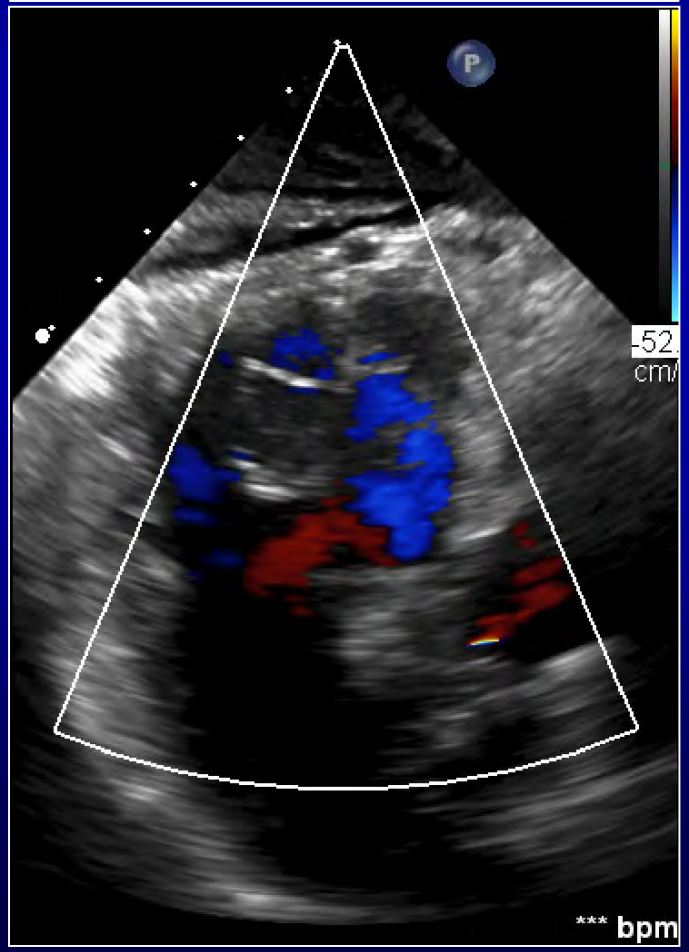
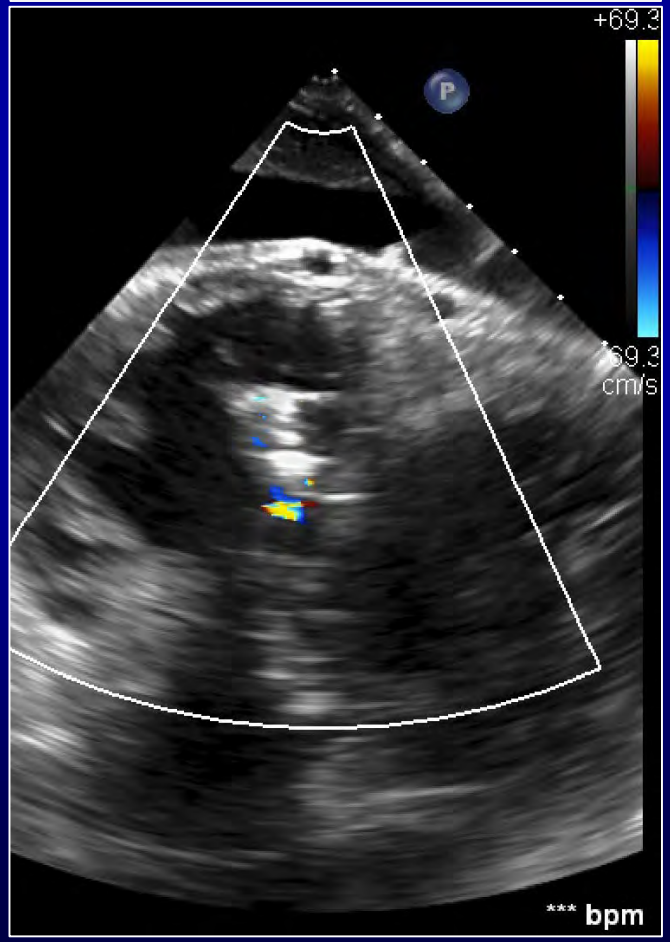
s/p 3 Clips

Baseline
Torrential TR



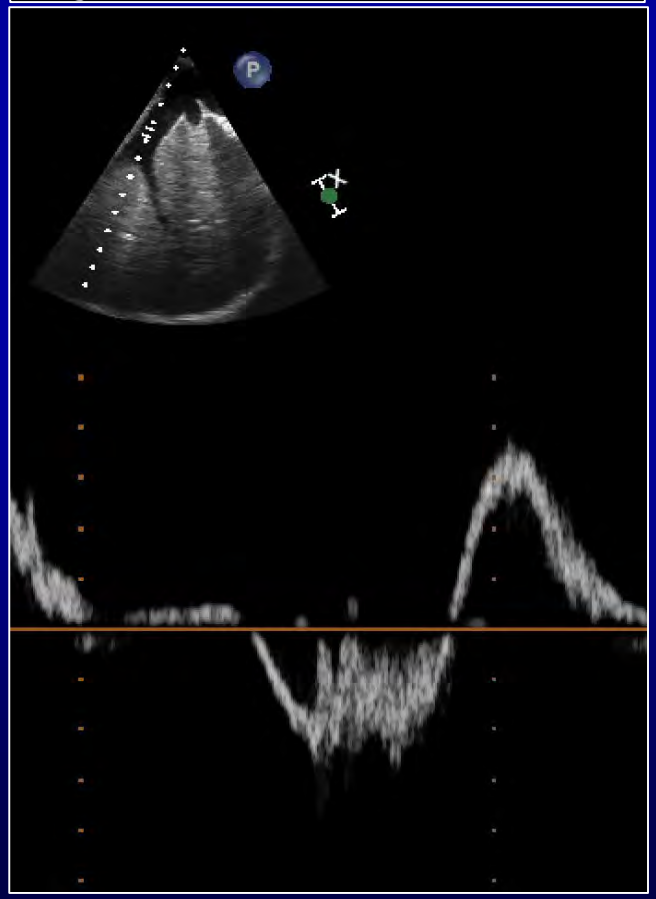
s/p 3 clips
Mild TR



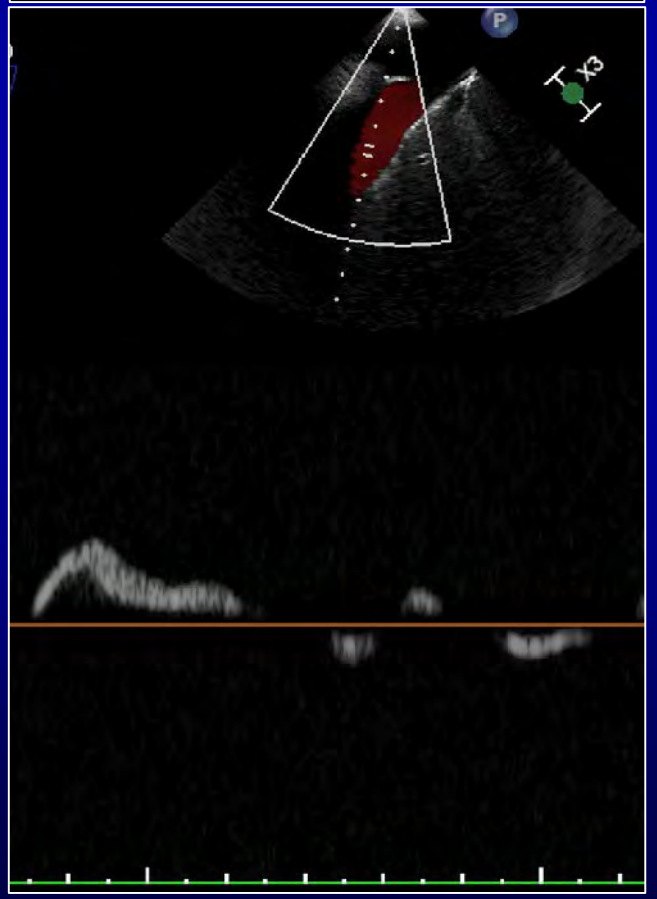
Patient readmitted 1 week later for heart failure
Brought to the cath lab for tricuspid clip

s/p 3 Clips

Baseline hepatic vein
Systolic flow reversal

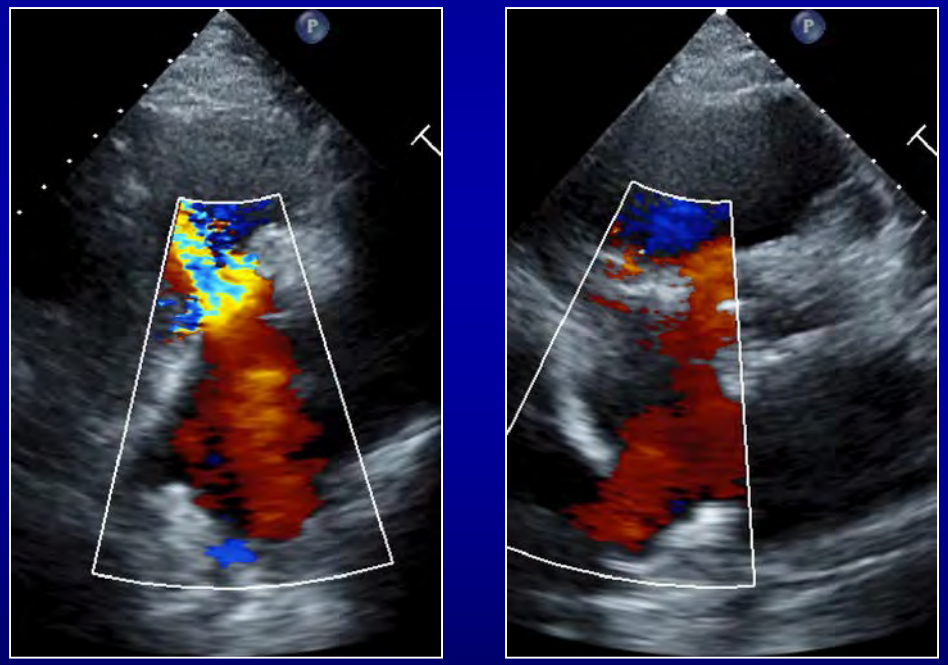


Final hepatic vein
Normal flow



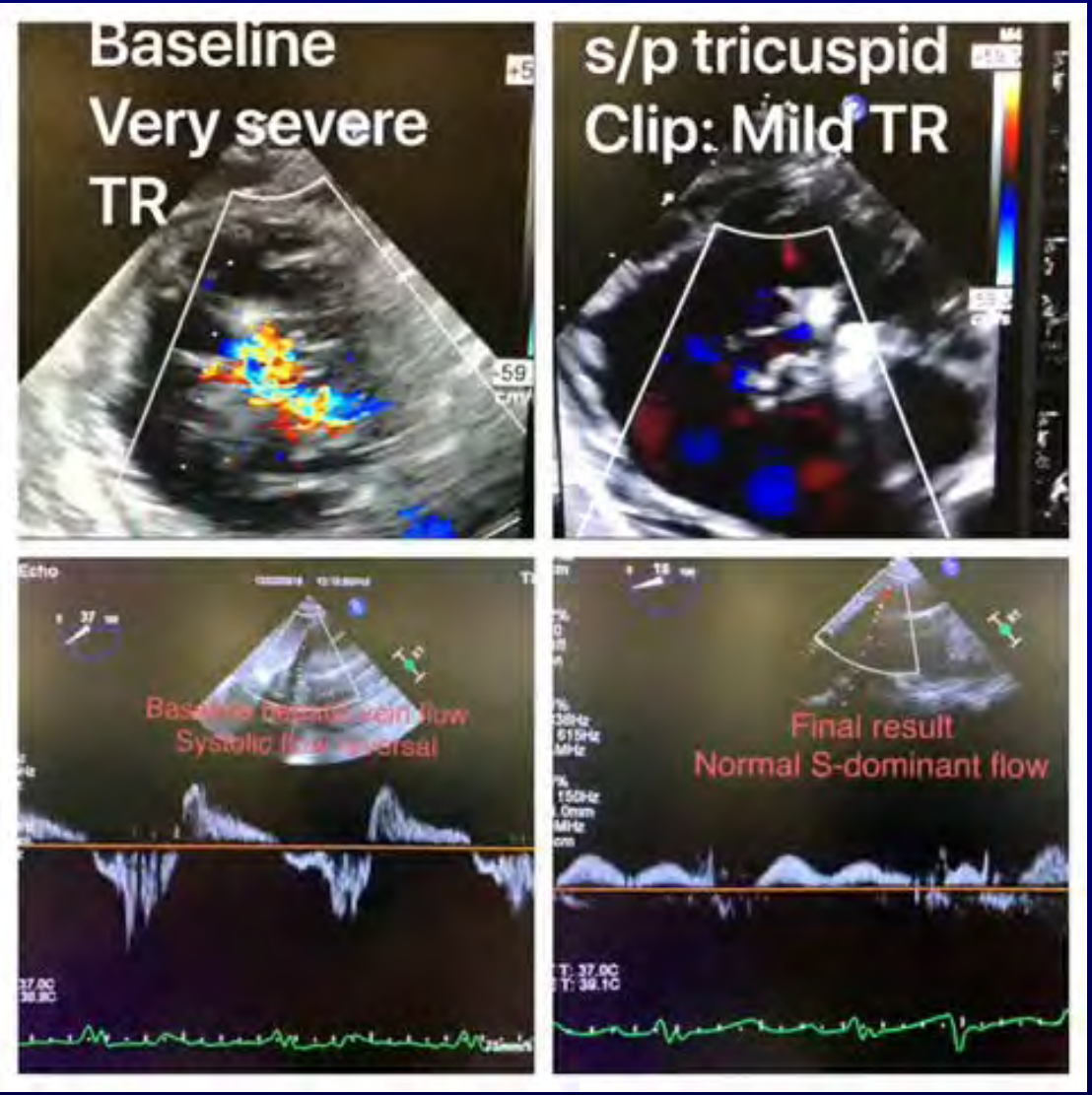
s/p tricuspid clip for 1 year

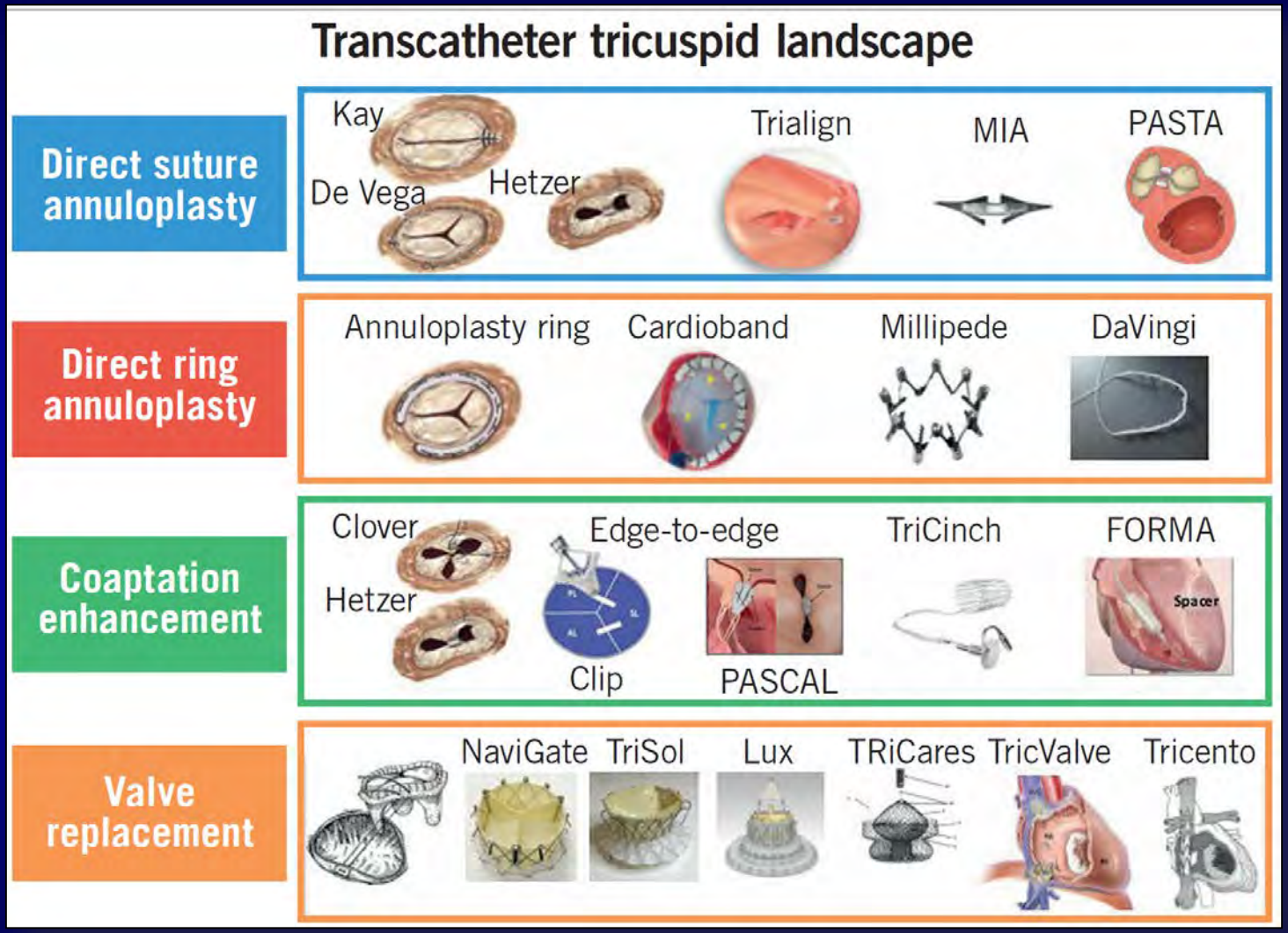
Mild tricuspid regurgitation



- Mild TR
- NYHA I
- Weight decreased from 214 →198 pounds
- No admissions for heart failure in 3 months
- *"I have not felt the same in the last 5 years"*
- Only 1 admission for heart failure in 1 year due to running out of lasix

Case example of severe TR in the presence of a pacemaker lead





A. Latib, F. Grigioni, RT Hahn. EuroIntervention 2018

Conclusions

- Transcatheter mitral valve repair with MitraClip is safe
- MitraClip is the standard of care for the treatment of degenerative MR in patients who are at elevated risk for open heart surgery
- MitraClip for the treatment of functional MR in patients with reduced EF results in decreased mortality, decreased heart failure hospitalizations, improved exercise capacity, improved quality of life and delay to LVAD/heart transplant.
- In patients who are not ideal candidates for MitraClip, there are multiple treatment options with the investigational devices for transcatheter mitral valve repair or replacement

Conclusions

- Transcatheter mitral valve replacement with balloon-expandable valves is feasible for failed mitral bioprosthetic valves, failed annuloplasty rings and degenerative mitral valves with mitral annular calcification
- MitraClip for the treatment of tricuspid regurgitation is an excellent emerging option for the treatment of symptomatic tricuspid regurgitation