Contemporary Management of Mitral Regurgitation

Tailoring Treatment to The Patient Subset & Clinical Situation

Hatim Al Lawati MD, FRCPC, FACC

Consultant | Interventional Cardiology

Sultan Qaboos University Hospital | Oman

hatim.al.lawati@gmail.com

Contemporary Management of Mitral Regurgitation
Tailoring Treatment to The Patient Subset & Clinical Situation

DISCLOSURES

I, Hatim Al Lawati, have no disclosures relevant to the topic of this presentation. All slides were prepared by myself without any external contribution.

Burden of valvular heart diseases
- a population-based study -

Prevalence of valvular heart diseases in population-based studies

	Age (years)			>15% with moderate or severe mitral regurgitation		p value for trend
	18–44	45–54	55–64	65–74	≥75	
Participants (n)	4351	696	1240	3879	1745	..
Male, n (%)	1959 (45%)	258 (37%)	415 (33%)	1586 (41%)	826 (47%)	..
Mitral regurgitation (n=449)	23, 0·5% (0·3–0·8)	1, 0·1% (0–0·8)	12, 1·0% (0·5–1·8)	250, 6·4% (5·7–7·3)	163, 9·3% (8·1–10·9)	<0·0001
Mitral stenosis (n=15)	0, 0% (0–0·1)	1, 0·1% (0–0·8)	3, 0·2% (0·1–0·7)	7, 0·2% (0·1–0·4)	4, 0·2% (0·1–0·6)	0·006
Aortic regurgitation (n=90)	10, 0·2% (0·1–0·4)	1, 0·1% (0–0·8)	8, 0·7% (0·3–1·3)	37, 1·0% (0·7–1·3)	34, 2·0% (1·4–2·7)	<0·0001
Aortic stenosis (n=102)	1, 0·02% (0–0·1)	1, 0·1% (0–0·8)	2, 0·2% (0·6–1·9)	50, 1·3% (1·0–1·7)	48, 2·8% (2·1–3·7)	<0·0001
Any valve disease						
Overall (n=615)	31, 0·7% (0·5–1·0)	3, 0·4% (0·1–1·3)	23, 1·9% (1·2–2·8)	328, 8·5% (7·6–9·4)	230, 13·2% (11·7–15·0)	<0·0001
Women (n=356)	19, 0·8% (0·5–1·3)	1, 0·2% (0·01–1·3)	13, 1·6% (0·9–2·7)	208, 9·1% (8·0–10·4)	115, 12·6% (10·6–15·0)	<0·0001
Men (n=259)	12, 0·6% (0·3–1·1)	2, 0·8% (0·1–2·8)	10, 2·4% (1·2–4·4)	120, 7·6% (6·3–9·0)	115, 14·0% (11·7–16·6)	<0·0001

Prevalence data are n, % (95% CI). Percentages are rounded to one decimal place.

Nkomo VT, et al. Lancet 2006; 368: 1005-1011

Outcomes in patients with untreated severe chronic mitral regurgitation

One year survival was **96.3 + 1.3 %** in operated patients vs. **88.2 + 2.5 %** in the non-operated patients (p=0.003)[1]

Patients with **primary mitral regurgitation** have an excess mortality rate of 6.3% per year[2]

Within 10-years, the incidence of atrial fibrillation is ~30% and incidence of clinical heart failure is 63%[2]

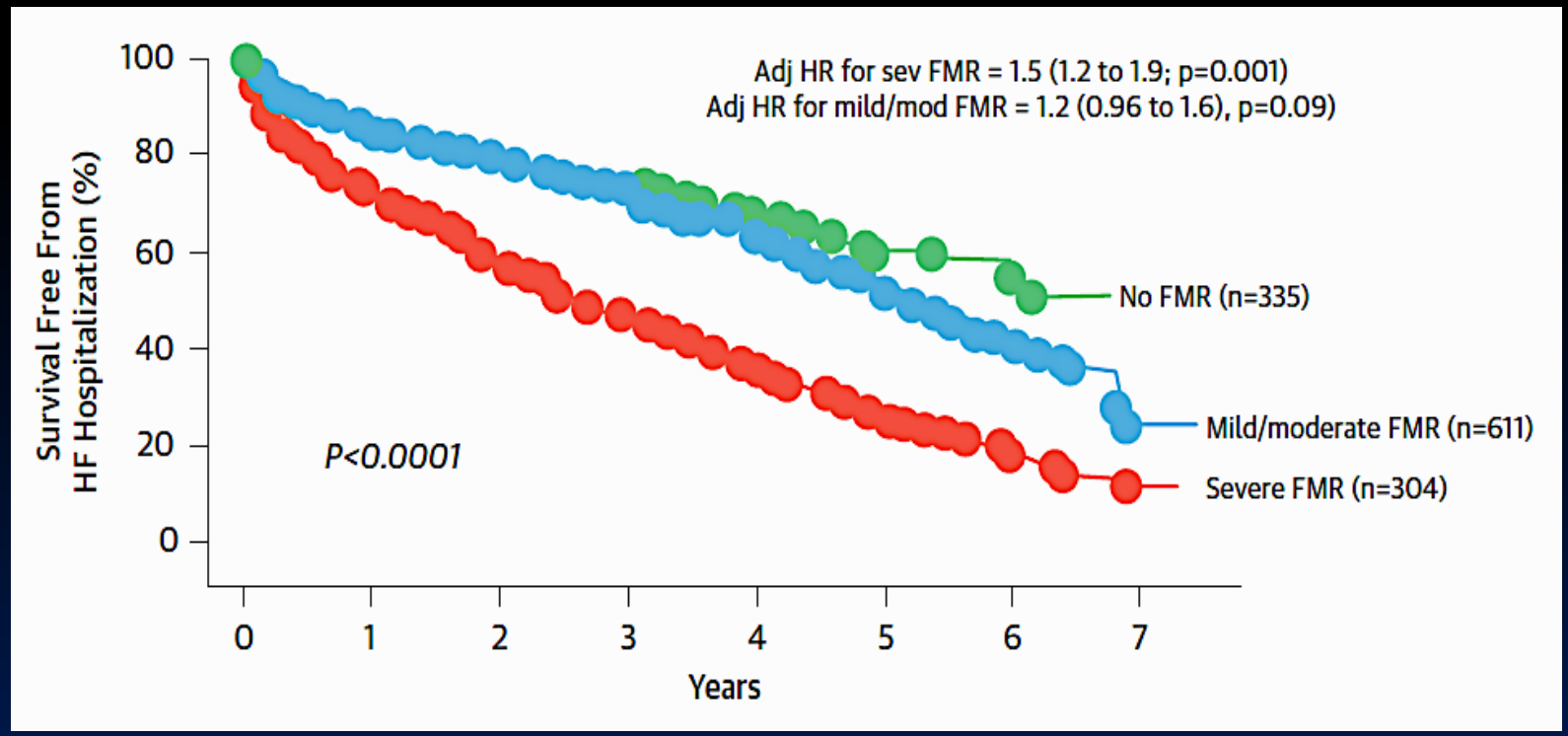
Sudden death accounts for ~25% of deaths in the symptomatic patients with severe mitral regurgitation on medical therapy[3]

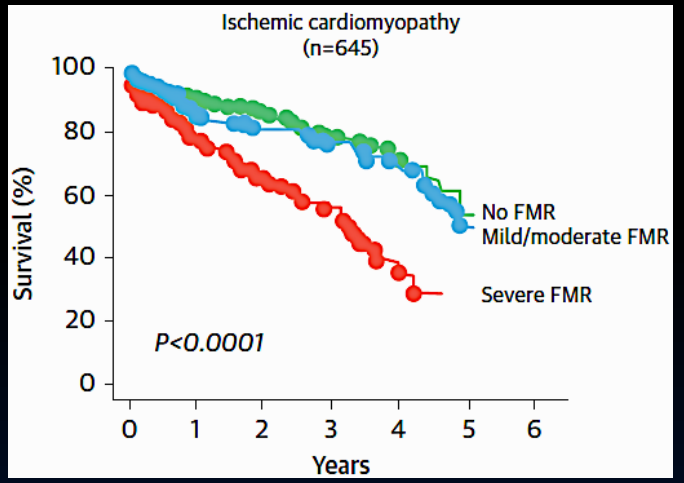
Patients with secondary (functional) mitral regurgitation (ischemic and non-ischemic) have increased incidence of adverse outcomes at smaller calculated regurgitation orifice area than for primary mitral regurgitation[4]

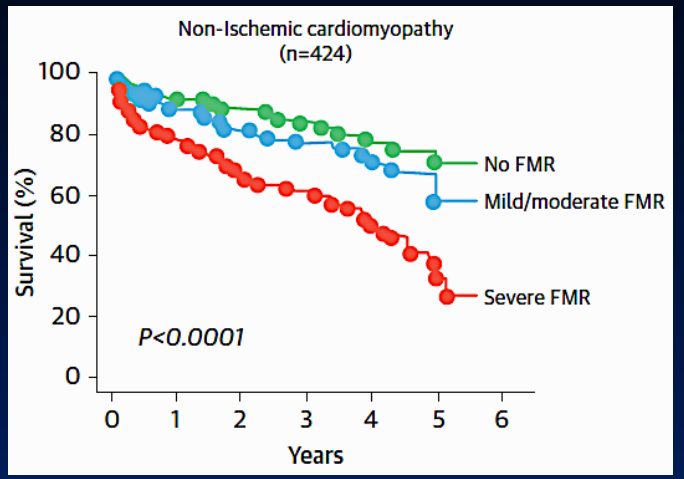
[1] Mirabel M, et al. Eur Heart J 2007; 28: 1358-1365
[2] Carabello BA. Mod Concepts Cardiovassc Dis 1988; 57: 53-58
[3] Grigioni F, et al. J Am Coll Cardiol 1999; 34: 2078-2085
[4] Nishimura RA, et al. Lancet 2016; 387: 1324-1334

Does the presence of 'functional' MR portend worse outcomes?

Prognosis of quantitatively determined secondary MR in patients with ischemic and non-ischemic cardiomyopathy







Asgar A, et al. J Am Coll Cardiol 2015; 65: 1231-1248

Recommendations for the treatment of chronic, severe primary mitral regurgitation

ACC/AHA guidelines on the management of valvular heart disease (2017 update)

Recommendation	COR	LOE
Mitral valve surgery is recommended for symptomatic patients with chronic severe primary MR and LVEF >30%	I	B
Mitral valve surgery is recommended for asymptomatic patients with chronic severe primary MR and LVEF 30-60% and/or LVESD ≥40 mm	I	B
Mitral valve repair is recommended in preference to MVR when surgical treatment is indicated for patients with chronic severe primary MR involving the AMVL or both leaflets when a successful and durable repair can be accomplished	I	B
Concomitant MV repair or MVR is indicated in patients with chronic severe primary MR undergoing cardiac surgery for other indications	I	B
Mitral valve repair is reasonable in asymptomatic patients with chronic severe primary MR with preserved LV (LVEF >60% and LVESD <40 mm) in whom the likelihood of a successful and durable repair without residual MR is >95% with <1% mortality	IIa	B

Recommendations for the treatment of chronic, severe primary mitral regurgitation

ACC/AHA guidelines on the management of valvular heart disease (2017 update)

Recommendation	COR	LOE
Mitral valve surgery is reasonable for asymptomatic patients with chronic severe primary MR and preserved LV function (LVEF >60% and LVESD <40 mm) with a progressive increase in LV size or decrease in LVEF on serial imaging studies	IIa	C
Mitral valve repair is reasonable for asymptomatic patients with chronic severe non-rheumatic primary MR with preserved LV function (LVEF >60 and LVESD <40 mm) in whom there is a high likelihood of a successful and durable repair with (1) new onset AF or (2) resting pulmonary hypertension (PASP >50 mmHg)	IIa	B
Mitral valve surgery may be considered in symptomatic patients with chronic severe primary MR and LVEF ≤30%	IIb	C
Transcatheter mitral valve repair may considered for severely symptomatic patients (NYHA class III to IV) with chronic severe primary MR who have favorable anatomy for repair procedure and a reasonable life expectancy but who have a **prohibitive surgical risk because of severe comorbidities and remain severely symptomatic despite optimal GDMT for heat failure**.	IIb	B

Recommendations for the treatment of chronic, severe Secondary mitral regurgitation

ACC/AHA guidelines on the management of valvular heart disease (2017 update)

Recommendation	COR	LOE
Mitral valve surgery is reasonable for patients with chronic severe secondary MR who are undergoing CABG or AVR	IIa	C
It is reasonable to choose chordal-sparing MVR over downsized annuloplasty repair if operation is considered for severely symptomatic patients (NYHA III to IV) with chronic severe ischemic MR and persistent symptoms despite GDMT for HF	IIa	B
Mitral valve repair or replacement may be considered for severely symptomatic patients (NYHA III to IV) with chronic severe secondary MR who have persistent symptoms despite optimal GDMT for HF	IIb	B
In patients with chronic, moderate, ischemic MR undergoing CABG, the usefulness of mitral valve repair is uncertain	IIb	B

Notice no recommendations for catheter-based mitral valve therapies in patients with chronic, severe, symptomatic secondary mitral regurgitation!!

Indications for intervention in severe primary mitral regurgitation

ESC guidelines on the management of valvular heart disease (2017)

Recommendation	COR	LOE
Mitral valve repair should be the preferred technique when the results are expected to be durable	I	C
Surgery is indicated in symptomatic patients with LVEF >30%	I	B
Surgery is indicated in asymptomatic patients with LV dysfunction (LVESD ≥45 mm and/or LVEF ≤60%)	I	B
Surgery should be considered in asymptomatic patients with preserved LV function (LVESD <45mm and LVEF >60%) and AF secondary to MR or pulmonary hypertension (PASP >50 mmHg)	IIa	B
Surgery should be considered in asymptomatic patients with preserved LVEF (>60%) and LVESD 40-45 mm when a durable repair is performed in a heart valve center and at least on of the following is present (1) flail leaflet or (2) presence of significant LA dilatation (volume index ≥60 ml/m^2 BSA) in sinus rhythm	IIa	C

Indications for intervention in severe primary mitral regurgitation

ESC guidelines on the management of valvular heart disease (2017)

Recommendation	COR	LOE
Mitral valve repair should be considered in symptomatic patients with severe LV dysfunction (LVEF <30% and/or LVESD >55 mm) refractory to GDMT when the likelihood of successful repair is low and comorbidity low	IIb	C
Mitral valve replacement may be considered in symptomatic patients with severe LV dysfunction (LVEF <30% and/or LVESD >55 mm) refractory to GDMT when the likelihood of successful repair is low and comorbidity low	IIb	C
Percutaneous edge-to-edge procedure may be considered in patients with symptomatic severe primary mitral regurgitation who fulfil the echocardiographic criteria for eligibility and are judged inoperable or at high risk by the heart team, avoiding futility	IIb	C

Indications for intervention in chronic secondary mitral regurgitation

ESC guidelines on the management of valvular heart disease (2017)

Recommendation	COR	LOE
Surgery is indicated in patients with severe secondary mitral regurgitation undergoing CABG and LVEF >30%	I	C
Surgery should be considered in symptomatic patients with severe secondary mitral regurgitation, LVEF <30% but with an option for revascularization and evidence of myocardial viability	IIa	C
When revascularization is not indicated, surgery may be considered in patients with severe secondary mitral regurgitation and LVEF >30% who remain symptomatic despite GDMT (including CRT if indicated) and have a low surgical risk	IIb	C
When revascularization is not indicated and surgical risk is not low, a percutaneous edge-to-edge procedure may be considered in patients with severe secondary mitral regurgitation and LVEF >30% who remain symptomatic despite GDMT (including CRT if indicated) and who have a suitable valve morphology by echocardiography avoiding futility	IIb	C
In patients with severe secondary mitral regurgitation and LVEF <30% who remain symptomatic despite GDMT (including CRT) and who have no option for revascularization, the heat team may consider percutaneous edge-to-edge procedure or valve surgery after careful evaluation for a ventricular assist device or heart transplantation according to individual patient characteristics	IIb	C

Re-operation rate vs. Recurrence of significant MR

Follow-up studies post standard surgical mitral valve repair technique comparing rates of re-operation and incidence of moderate to severe mitral regurgitation at the last documented follow-up

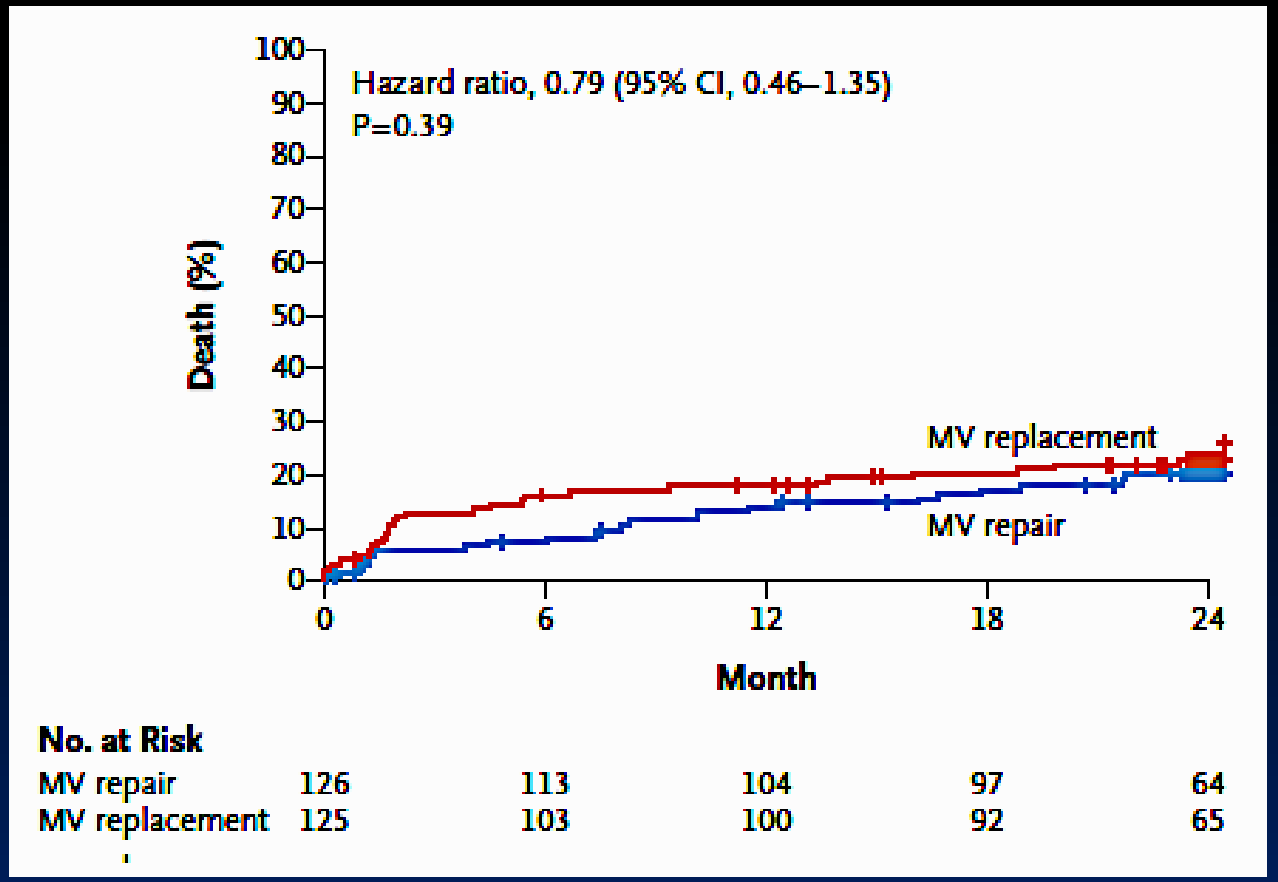
Study/Author	N	Surgical Technique	Re-operation rate % at latest follow-up (yr)	% MR ≥3+ at latest follow-up (yr)
Gallinov, et al. *Ann Thorac Surg 2000*	197	Carpentier*	5% (5 yr)	9% (1.5 yr)
Tanaka. et al. *Am J Cardiol 2003*	191	Carpentier*	5.3% (3.7 yr)	7% (3.5 yr)
Flameng, et al. *Circulation 2003*	242	Carpentier*	5.8% (7 yr)	29% (7 yr).

**Standard repair with annuloplasty in the vast majority of cases.*

Is mitral valve repair truly the ultimate ”panacea”?

Two-Year Outcomes of Surgical Treatment of Severe Ischemic Mitral Regurgitation

Time-to-Event curves for death. The most frequent underlying cause s of death were multisystem organ failure (in 20.8% of patients), Heart failure (in 17.0%) and sepsis (in 13.2%)

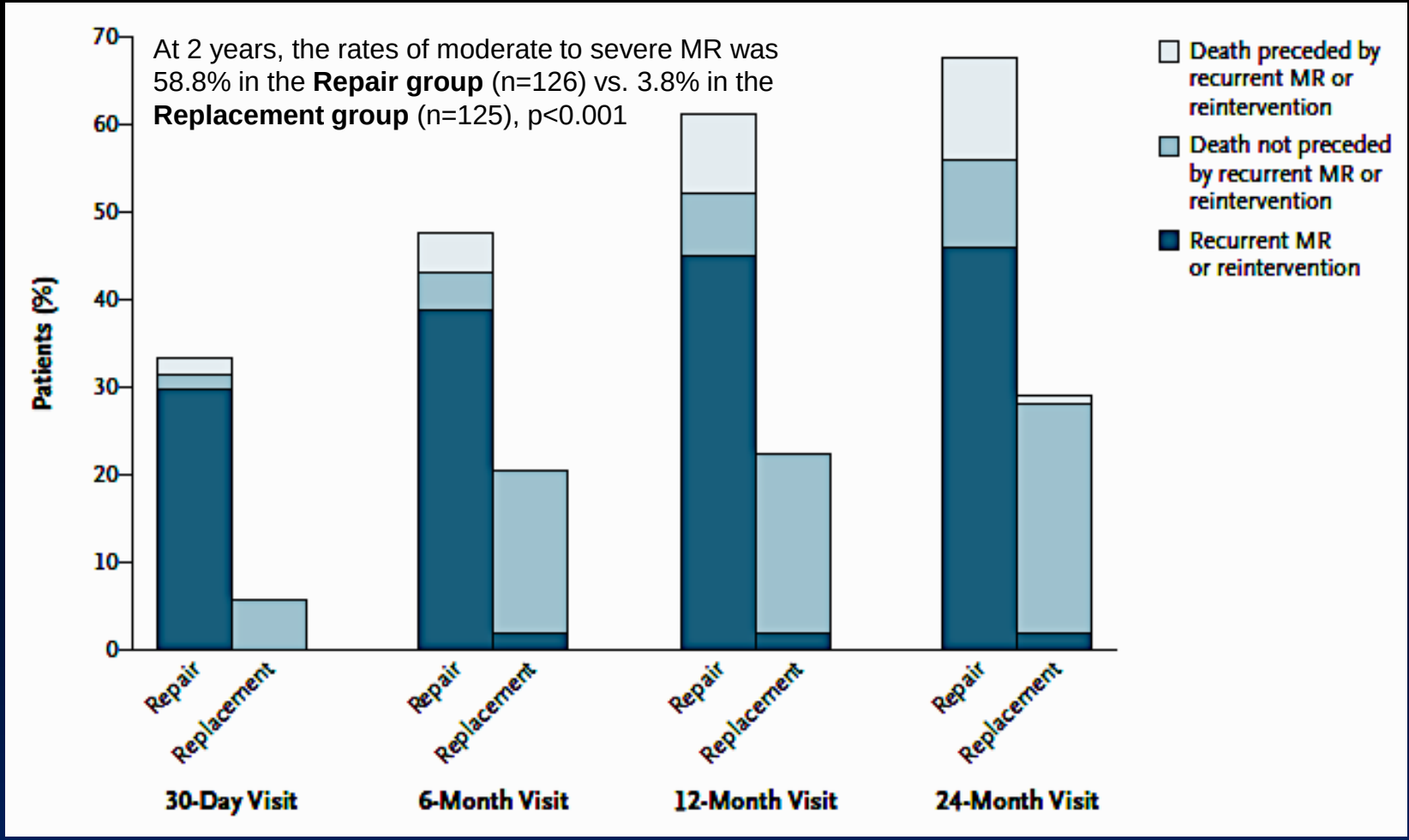


Goldstein D, et al. N Engl J Med 2016; 374: 344-353

Is mitral valve repair truly the ultimate ”panacea”?

Two-Year Outcomes of Surgical Treatment of Severe Ischemic Mitral Regurgitation

Cumulative failure of Mitral-Valve repair or replacement.



Goldstein D, et al. N Engl J Med 2016; 374: 344-353

Is mitral valve repair truly the ultimate ”panacea”?

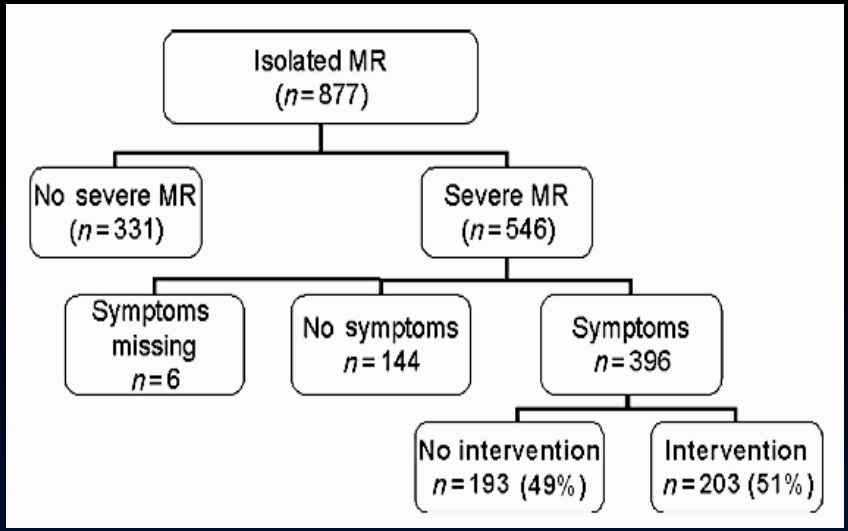
Clinical end points, serious adverse events, and hospitalizations at 2 years

Variable	Repair (N=126)	Replacement (N=125)	P Value*
	no./total no. of patients (%)		
Clinical end point			
Death	24/126 (19.0)	29/125 (23.2)	0.42
Stroke	10/126 (7.9)	7/125 (5.6)	0.46
Worsening New York Heart Association class†	5/85 (5.9)	5/84 (6.0)	1.0
Rehospitalization for heart failure	27/126 (21.4)	22/125 (17.6)	0.44
Failed index mitral-valve procedure	6/126 (4.8)	0	0.03
Mitral-valve reoperation	4/126 (3.2)	1/125 (0.8)	0.37
Moderate or severe recurrent mitral regurgitation	57/97 (58.8)	3/79 (3.8)	<0.001
MACCE‡	53/126 (42.1)	53/125 (42.4)	0.96
Canadian Cardiovascular Society class III or IV	4/82 (4.9)	0/80	0.19
	no. of events (rate/100 patient-yr)		

Goldstein D, et al. N Engl J Med 2016; 374: 344-353

Characteristics of patients with severe, symptomatic, mitral regurgitation who are denied surgery

Analysis from the Euro Heart Survey



One year survival was **96.3 + 1.3 %** in operated patients vs. **88.2 + 2.5 %** in the non-operated patients (p=0.003)

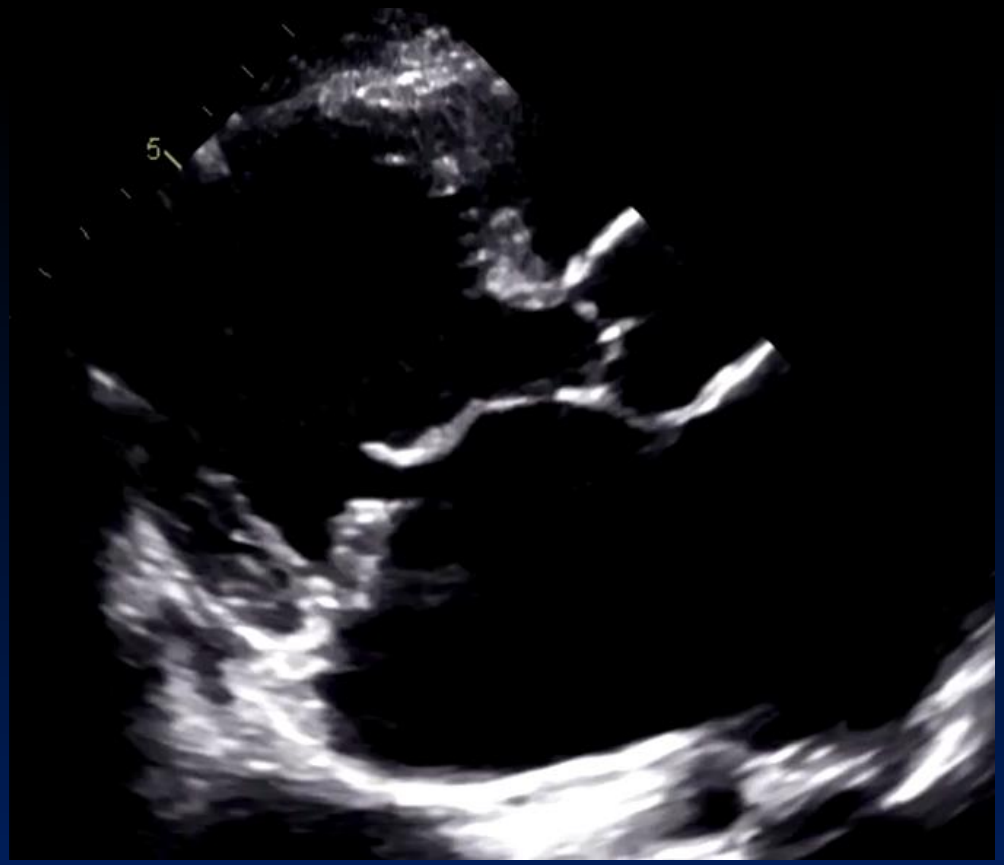
Factors associated with a decision not to operate – Multivariate Analysis

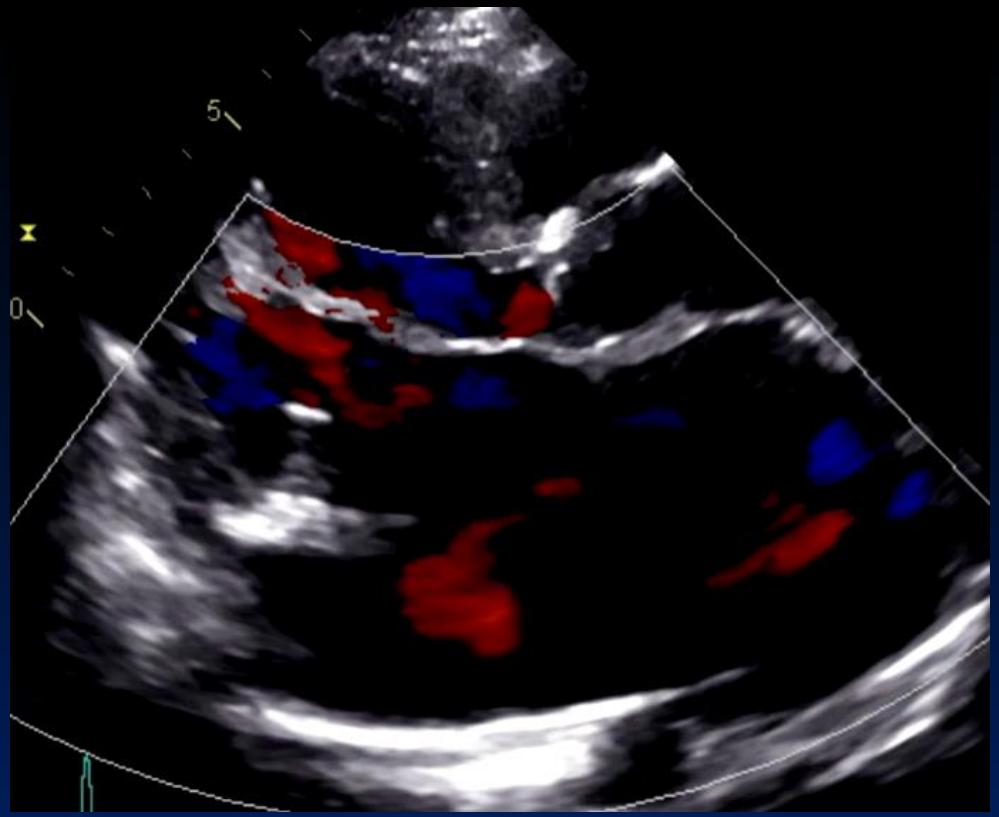
	P	Odds ratio	95% CI
LVEF (per 10% decrease)	0.0002	1.39	(1.17-1.66)
Aetiology - Ischemic - Non-ischemic	0.0006	 1 4.44	 (1.96-10.76)
Age (per 10-year increase)	0.001	1.40	(1.15-1.72)
Charlson comorbidity index (per 1 point increase)	0.004	1.38	(1.12-1.72)
Degree of Mitral Regurgitation - Grade 4/4 - Grade 3/4	0.005	 1 2.23	 (1.28-3.29)

Mirabel M, et al. Eur Heart J 2007; 28: 1358-1365

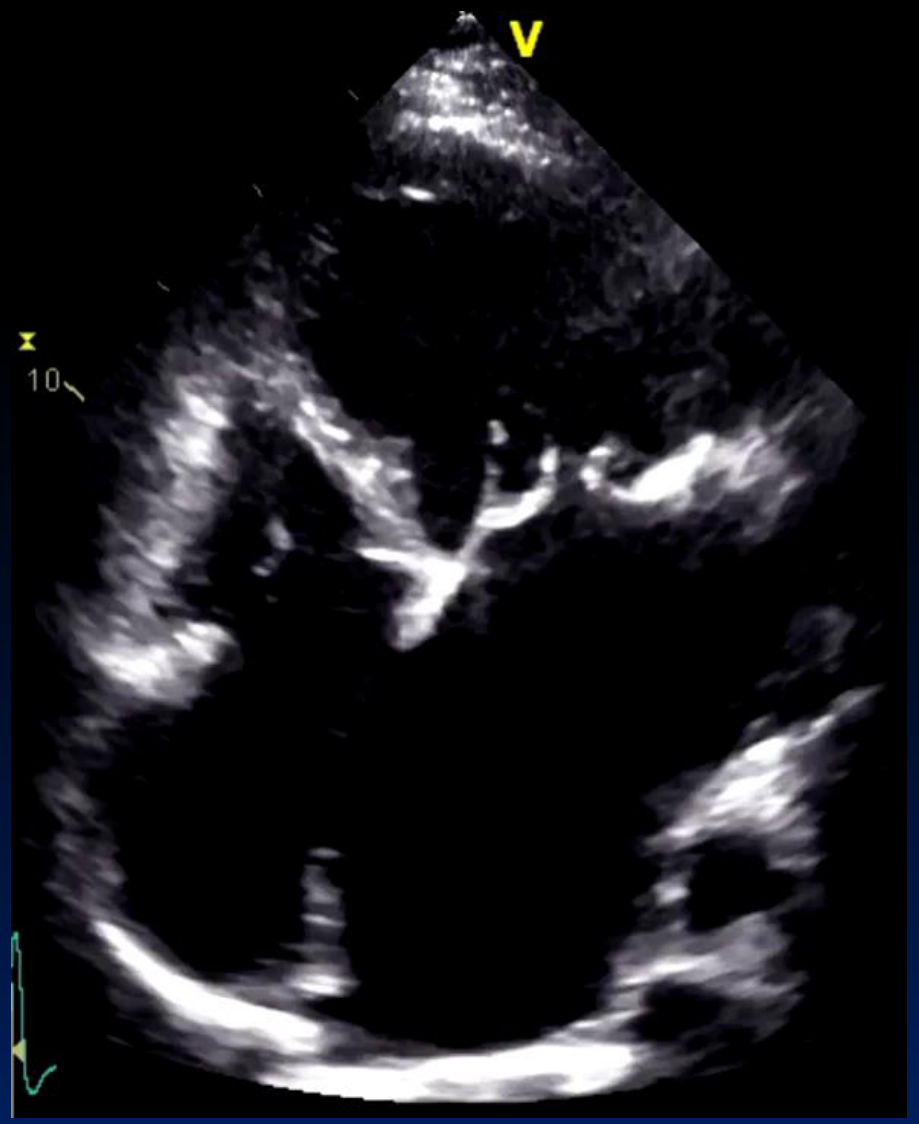
- Case (1) -

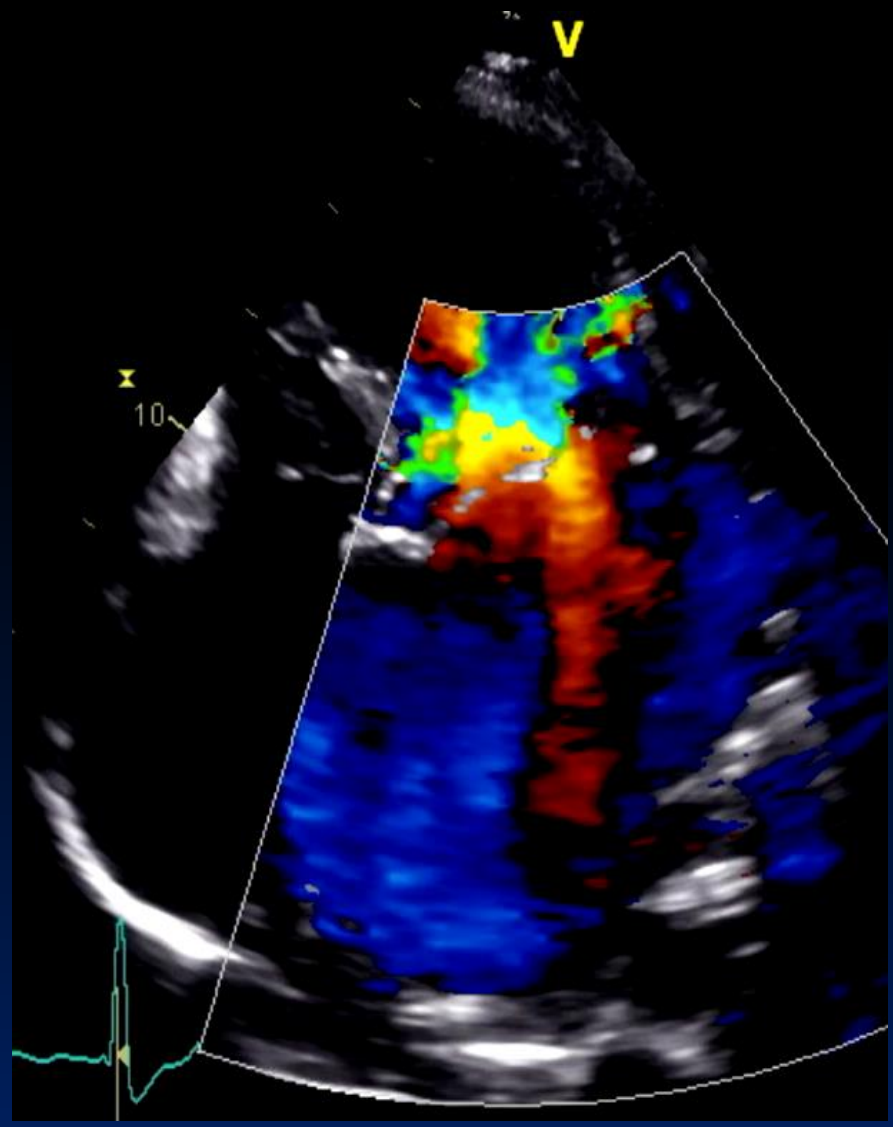
67-year-old female with hypertension, diabetes, chronic kidney disease (eGFR= 25 ml/min), permanent AF, prior ischemic stroke with residual right sided motor weakness, recurrent hospitalizations for decompensated HF, severe pulmonary hypertension (PASP ~65 mmHg on 2D transthoracic echocardiography)



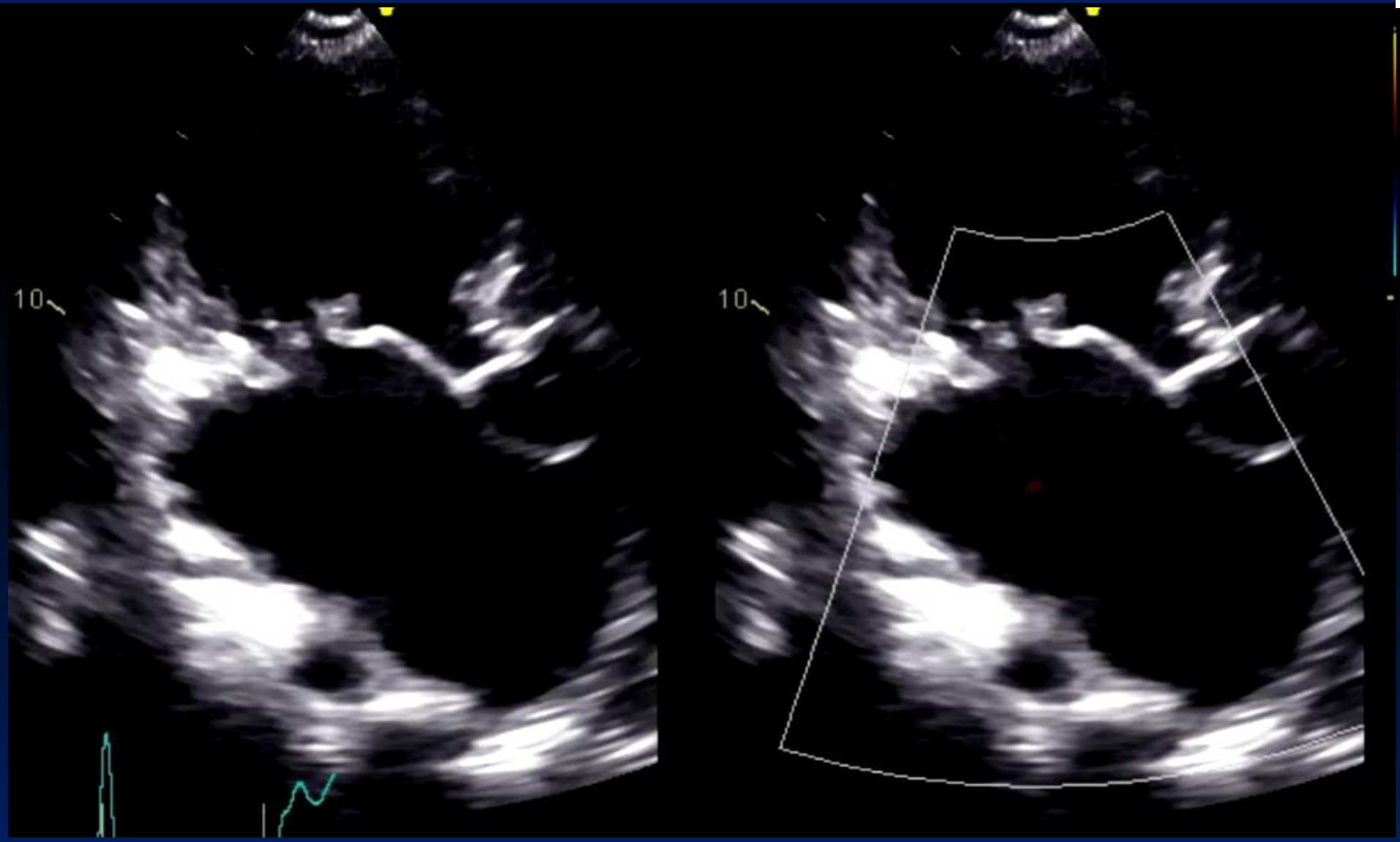


- Case (1) -

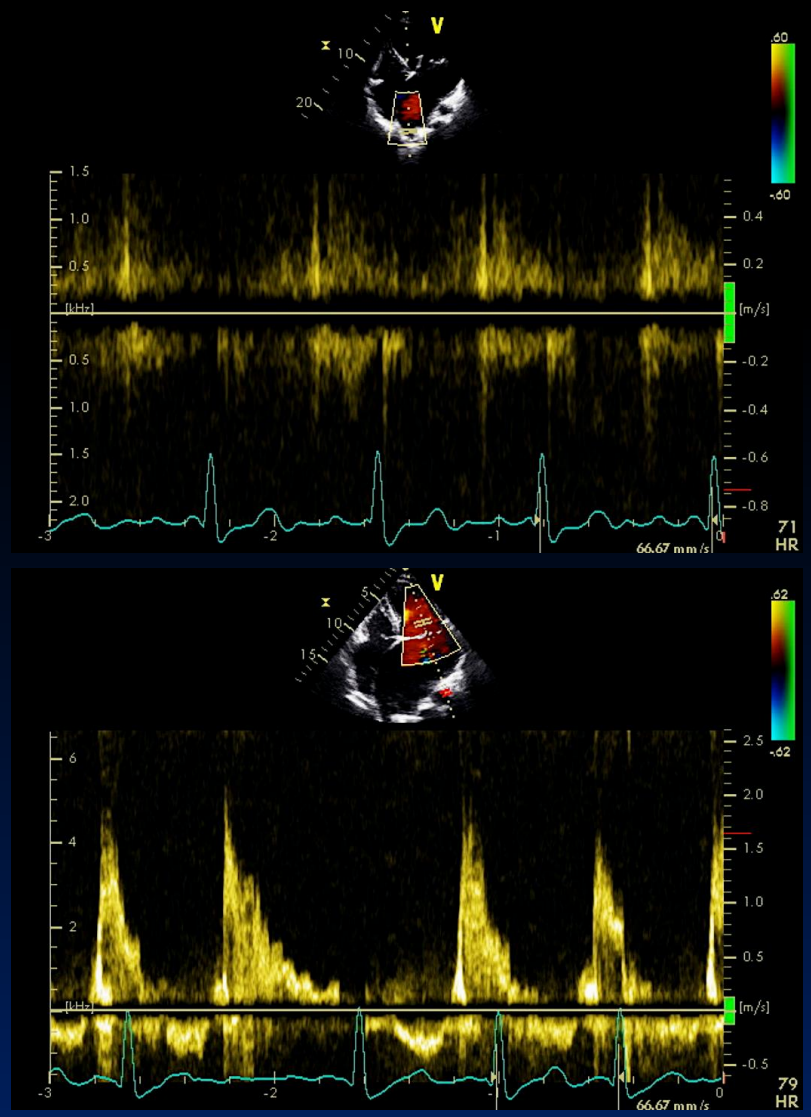


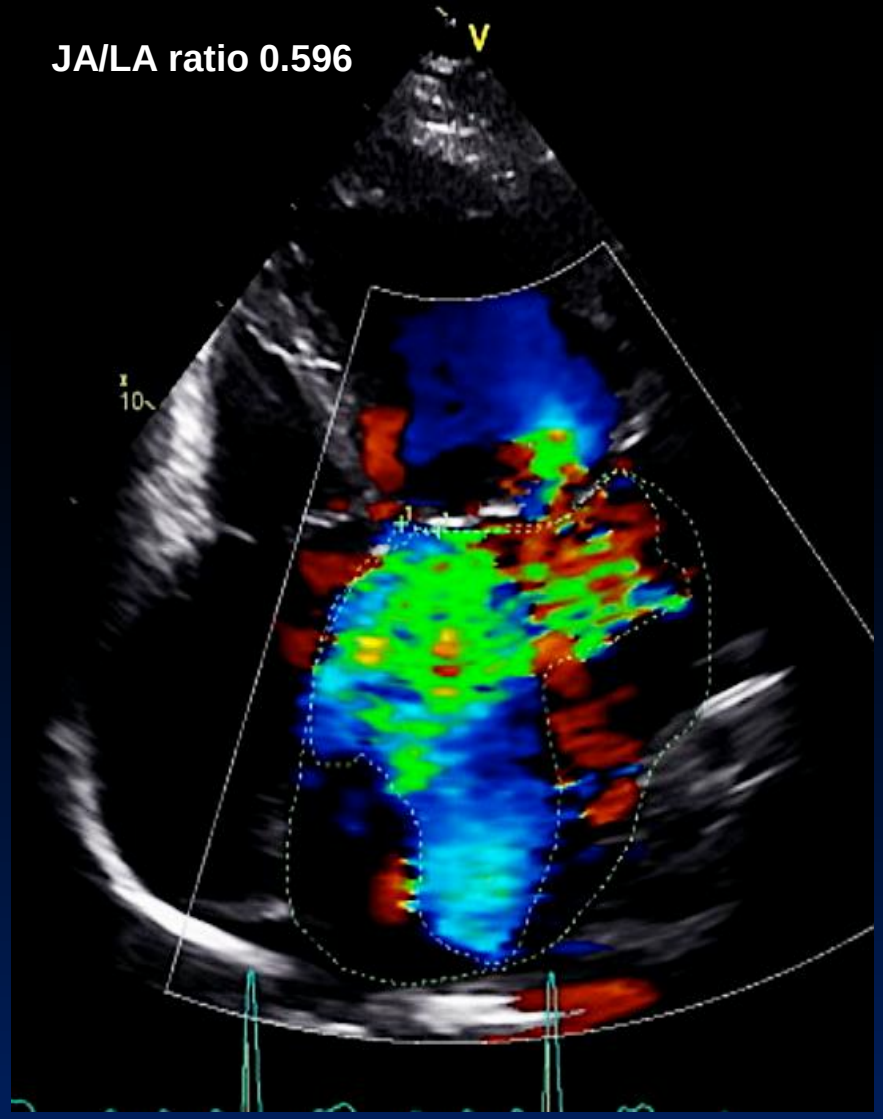


- Case (1) -



- Case (1) -

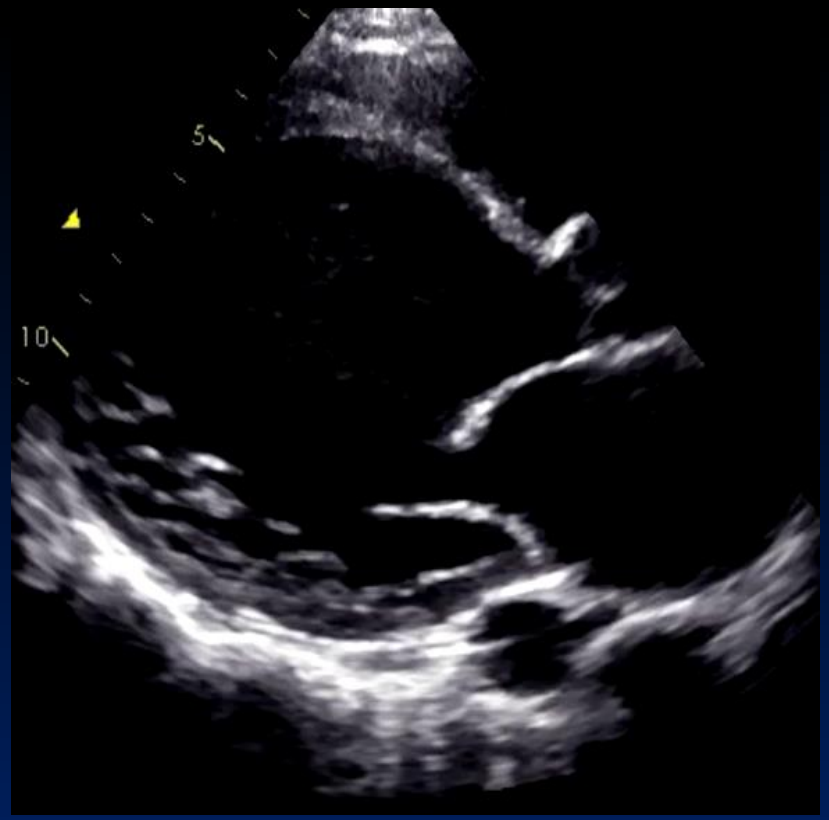


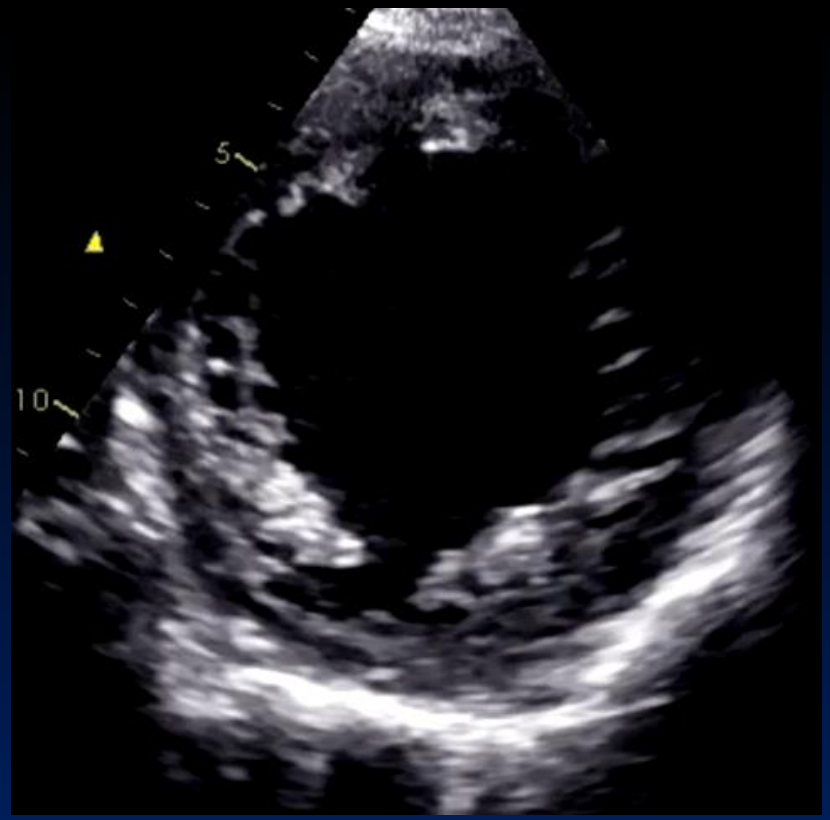


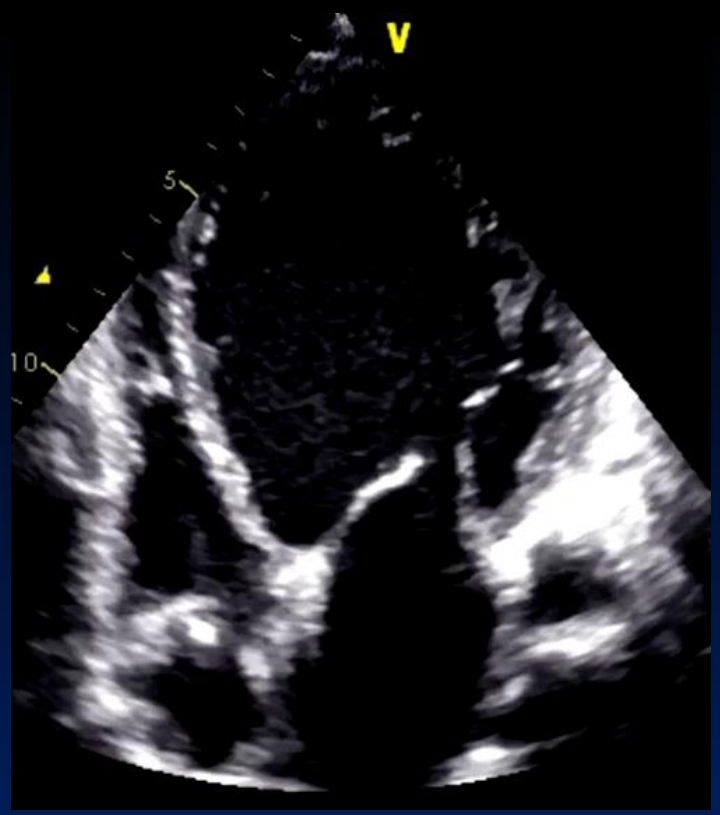
RF 63%
RV 84 mL
RoA 0.65 cm^2

- Case (2) -

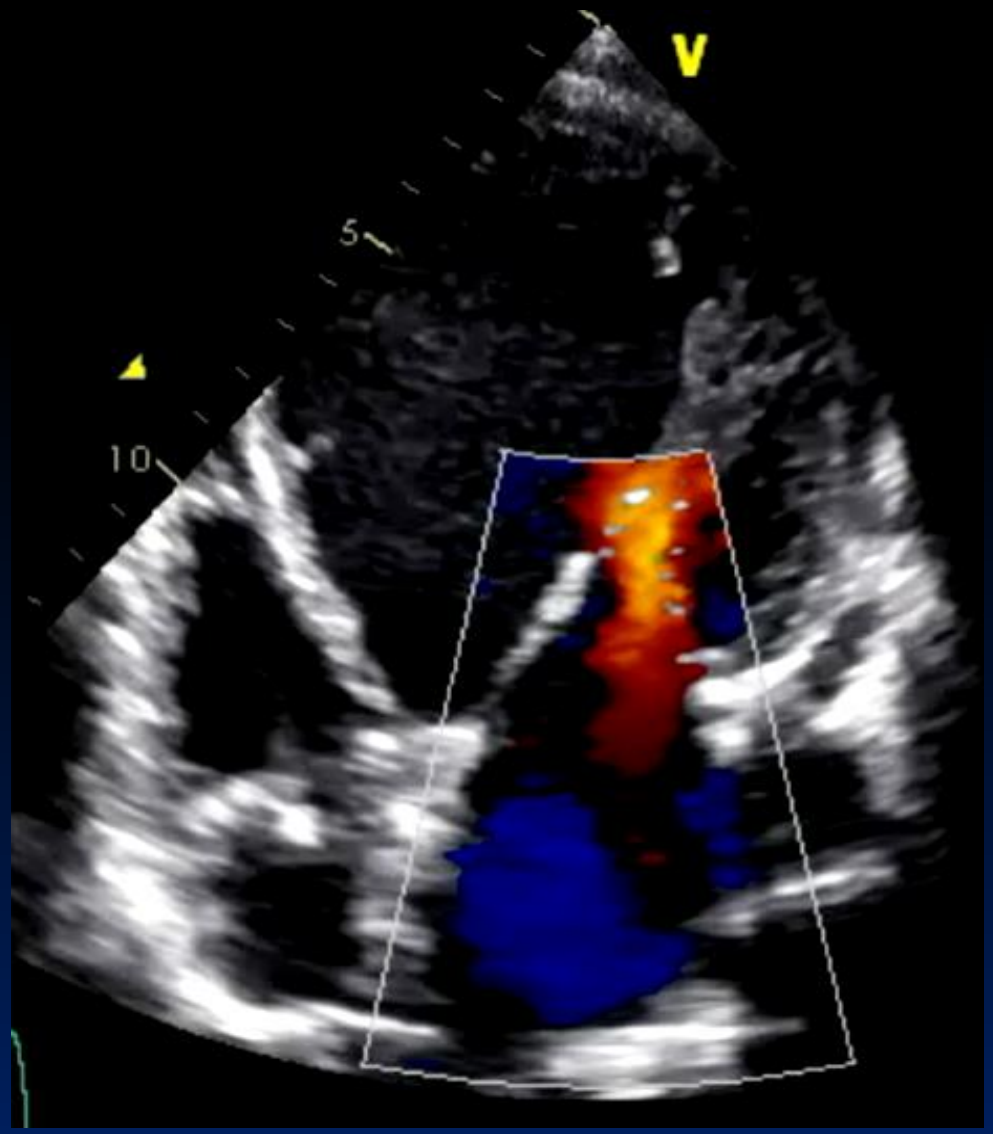
55-year-old female with non-ischemic dilated cardiomyopathy with severe LV systolic dysfunction (LVEF ~20%), chronic kidney disease (eGFR= 35 ml/min), permanent AF, prior VF arrest post CRT-D implantation, recurrent hospitalizations for decompensated HF despite optimal GDMT, severe pulmonary hypertension (mean PA pressure 50 mmHg from right heart catheterization)

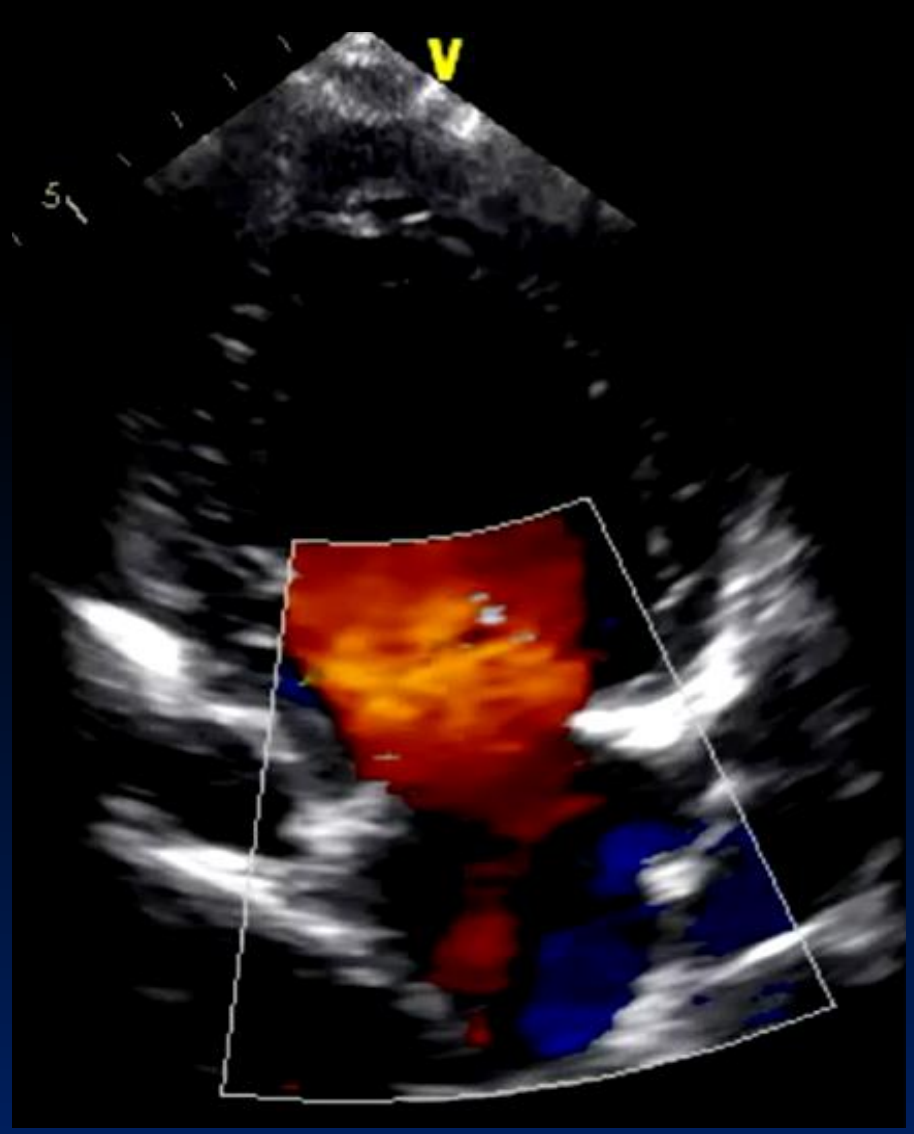






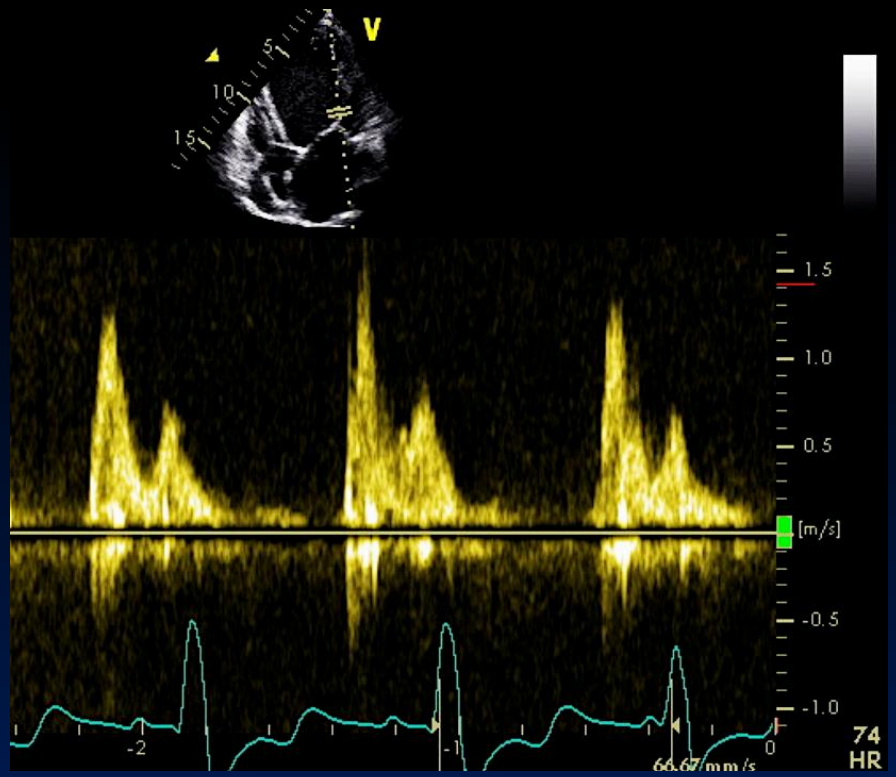
- Case (2) -



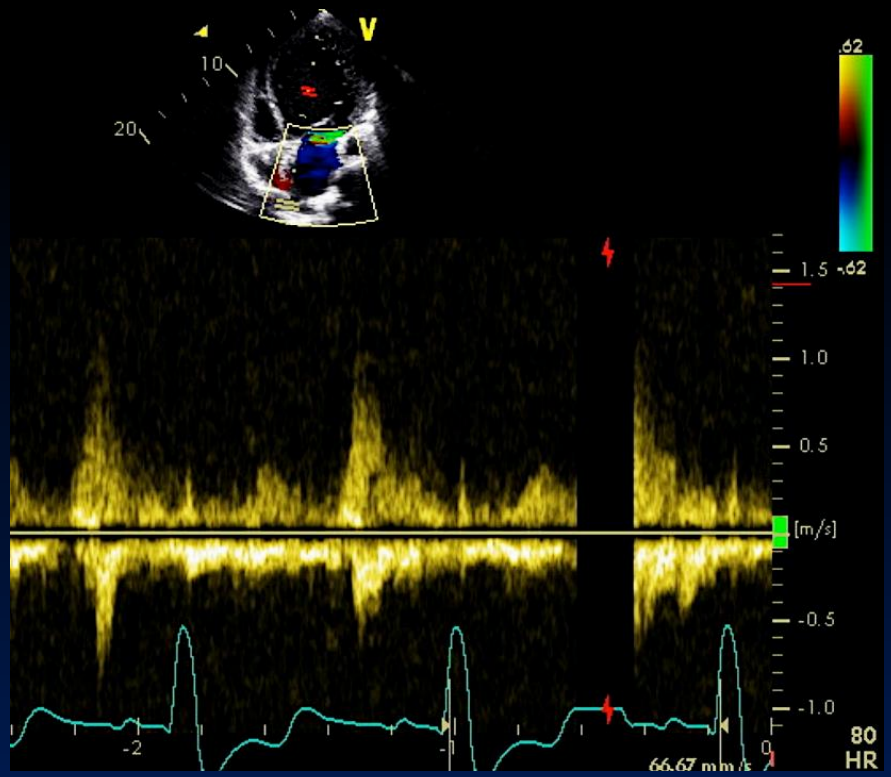


- Case (1) -

MV inflow velocity



PV doppler flow & velocities



RF 55%
RV 60 mL
RoA 0.43 cm^2

Transcatheter Mitral Valve Repair/Replacement

- Device Landscape 2017 -

Edge-to-Edge

MitraClip
MitraFlex

Direct annuloplasty and basal ventriculoplasty

Mitralign Bident
GDS Accucinch
Valtech Cardioband
Quantum Cor (RF)
Micardia enCor

Coronary sinus annuloplasty

Cardiac Dimensions
Carillon
Cerclage
annuloplasty

MV replacement

CardiAQ
Neovasc
Edwards Fortis
Micro Interventional
Valtech Cardiovalve
Valve Xchange
Lutter Valve
Medtronic
Tendyne
MitrAssist
Mvalve

Other approaches

MitraSpacer
St. Jude leaflet plication
Cardiac Implant perc ring
NeoChord
Babic chords
Valtech Vchordal
Middle Peak Medical
Mardil BACE
Mitralis
Millipede

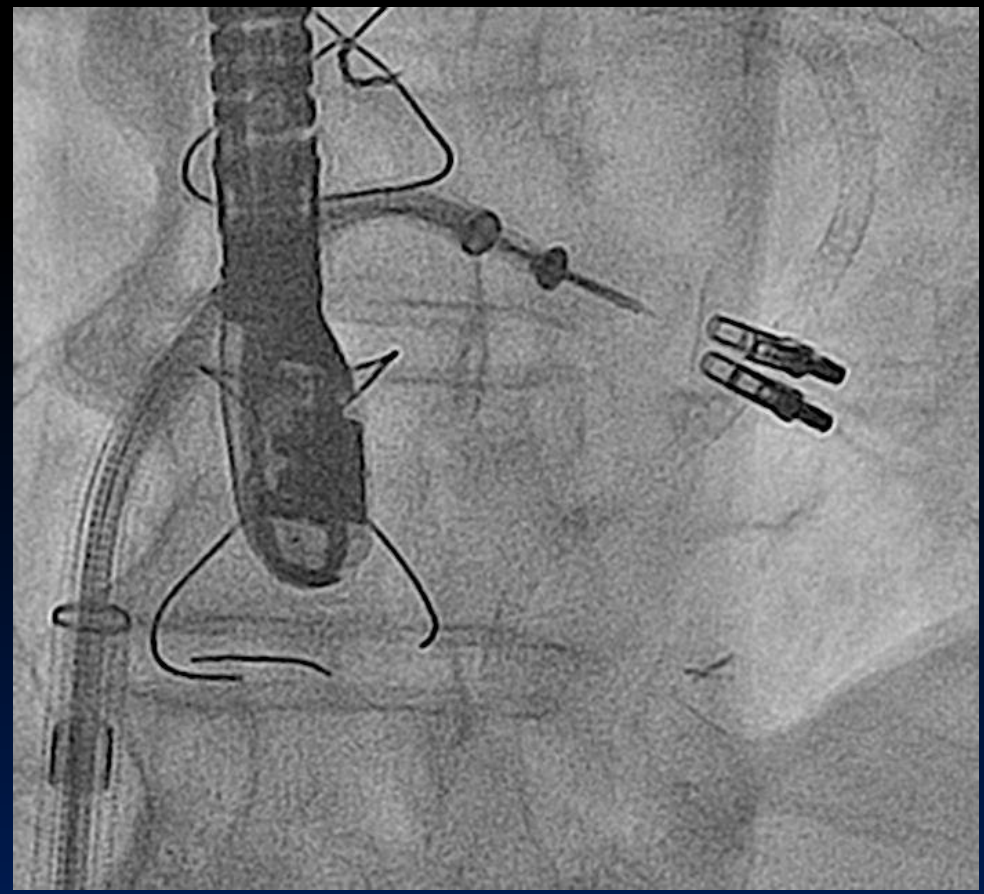
Transcatheter Mitral Valve Repair

- Edge-to-Edge Leaflet Repair -

>50,000 implants worldwide

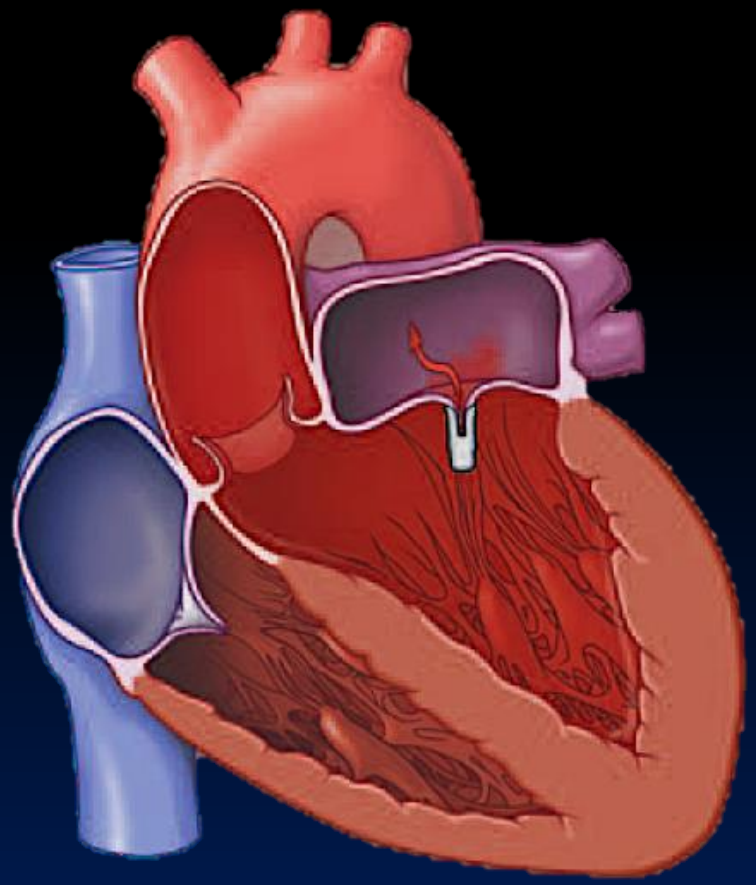
MitraClip®
MitraClip®-NT

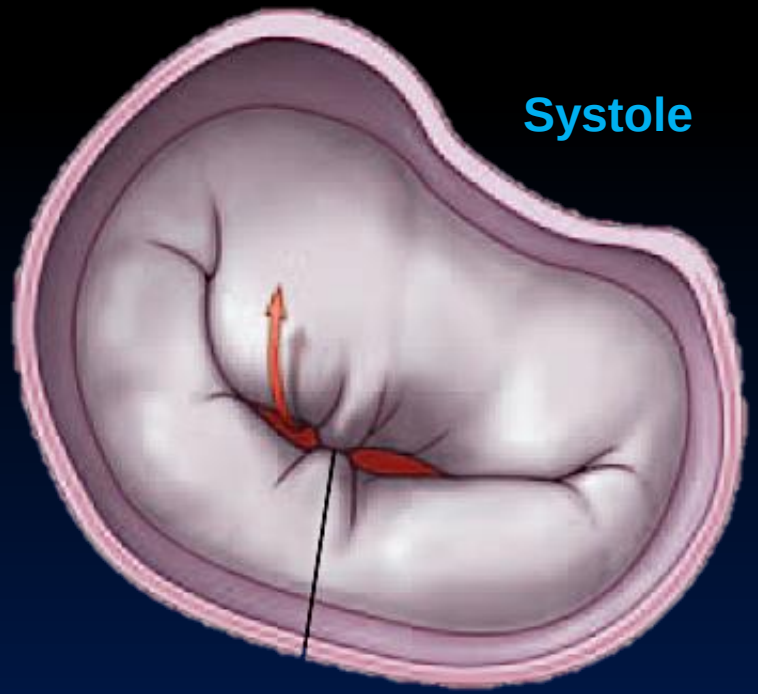
(Abbott Vascular, Santa Clara, CA, USA)

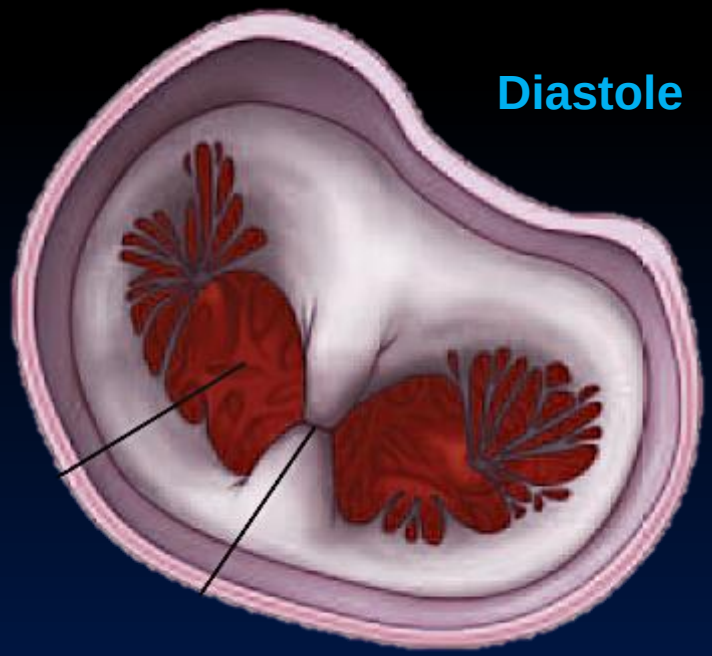


Transcatheter Mitral Valve Repair

- Edge-to-Edge Leaflet Repair -







Feldman T, et al. N Engl J Med 2011; 364: 1395-1406

Percutaneous Repair or Surgery for Mitral Regurgitation

- The EVEREST II Trial -

Primary efficacy end point at 12 months and major adverse events at 30 days in the intention-to-treat population

Event	Percutaneous Repair	Surgery	P Value
	no. (%)		
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

**Note that in the surgical group, 20% of the patients with complete follow-up data had significant (Grade ≥3+) mitral regurgitation at 12 months!*

Feldman T, et al. N Engl J Med 2011; 364: 1395-1406

Percutaneous Repair or Surgery for Mitral Regurgitation

- The EVEREST II Trial -

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
Death	2 (1)	2 (2)	0.89
Myocardial infarction	0	0	NA
Reoperation for failed surgical repair or replacement	0	1 (1)	0.74
Urgent or emergency cardiovascular surgery for adverse event	4 (2)	4 (4)	0.57
Major stroke	2 (1)‖	2 (2)	0.89
Renal failure	1 (<1)	0	1.00
Deep wound infection	0	0	NA
Mechanical ventilation for >48 hr	0	4 (4)	0.02
Gastrointestinal complication requiring surgery	2 (1)	0	0.78
New onset of permanent atrial fibrillation	2 (1)	0	0.78
Septicemia	0	0	NA
Transfusion of ≥2 units of blood	24 (13)	42 (45)	<0.001

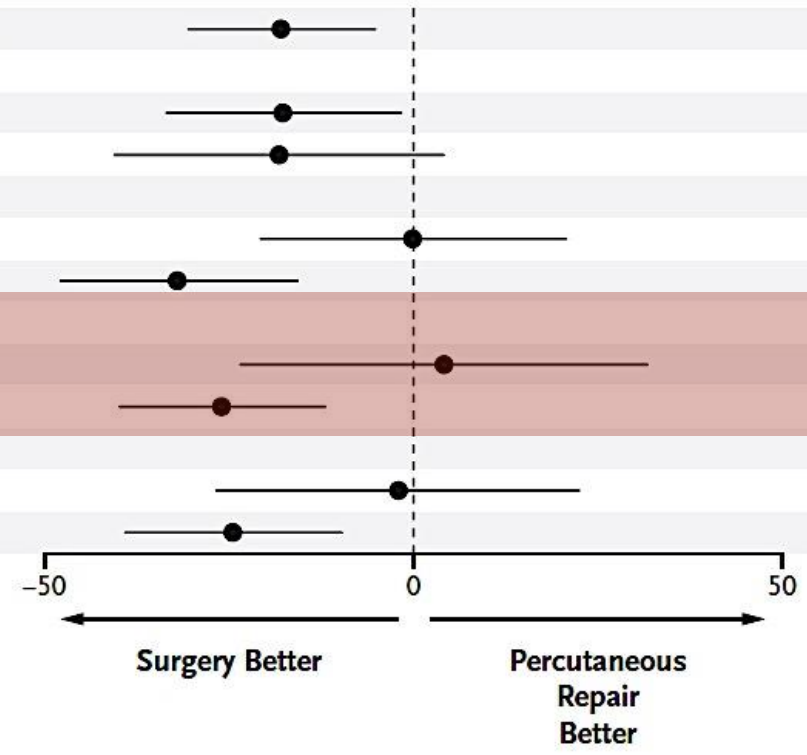
Feldman T, et al. N Engl J Med 2011; 364: 1395-1406

Percutaneous Repair or Surgery for Mitral Regurgitation

- The EVEREST II Trial -

Subgroup analyses for the primary end point at 12 months. Shown are the difference in rates of the primary efficacy endpoint (freedom from death, from mitral valve surgery, and from grade 3+ to 4+ mitral regurgitation) between patients in the percutaneous repair group and those in the surgery group for all randomized patients

Subgroup	Percutaneous Repair	Surgery	P Value for Interaction
	no. of events/total no. (%)		
All patients	100/181 (55)	65/89 (73)	
Sex			0.97
Male	63/114 (55)	43/59 (73)	
Female	37/67 (55)	22/30 (73)	
Age			0.009
≥70 yr	52/86 (60)	23/38 (61)	
<70 yr	48/95 (51)	42/51 (82)	
MR			
Functional	26/48 (54)	12/24 (50)	0.02
Degenerative	74/133 (56)	53/65 (82)	
LVEF			0.06
<60%	35/68 (51)	15/28 (54)	
≥60%	64/111 (58)	50/61 (82)	



Feldman T, et al. N Engl J Med 2011; 364: 1395-1406

Percutaneous Repair or Surgery for Mitral Regurgitation

- The EVEREST II Trial -

Secondary End points at 12 months in the intention-to-Treat population

- Effects on LV remodeling as studies on echocardiography -

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. N Engl J Med 2011; 364: 1395-1406

Percutaneous Repair or Surgery for Mitral Regurgitation

- The EVEREST II Trial -

Secondary End points at 12 months in the intention-to-Treat population

- Effects on Quality of Life measures -

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 quality-of-life score†							
30 days							
Physical component summary	147	3.1±9.4	<0.001	64	−4.9±13.3	0.004	<0.001
Mental component summary	148	4.4±11.3	<0.001	64	1.8±13.4	0.29	0.14
12 months							
Physical component summary	132	4.4±9.8	<0.001	60	4.4±10.4	0.002	0.98
Mental component summary	133	5.7±9.9	<0.001	60	3.8±10.3	0.006	0.24

Feldman T, et al. N Engl J Med 2011; 364: 1395-1406

Percutaneous Repair or Surgery for Mitral Regurgitation

- The EVEREST II Trial -

Secondary End points at 12 months in the intention-to-Treat population

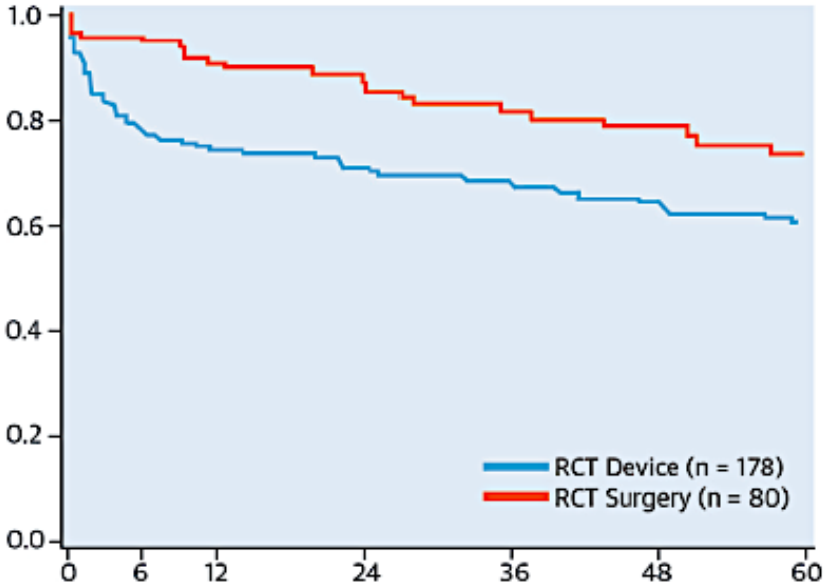
- Effects on Quality of Life measures -

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	
Severity of mitral regurgitation at 12 mo — no. (%)	153			69			<0.001
0+ (none)		9 (6)	NA		13 (19)	NA	
1+ (mild)		57 (37)	NA		39 (57)	NA	
1+ to 2+ (mild to moderate)		18 (12)	NA		5 (7)	NA	
2+ (moderate)		41 (27)	NA		9 (13)	NA	
3+ (moderate to severe)		21 (14)	NA		3 (4)	NA	
4+ (severe)		7 (5)	NA		0	NA	

Feldman T, et al. N Engl J Med 2011; 364: 1395-1406

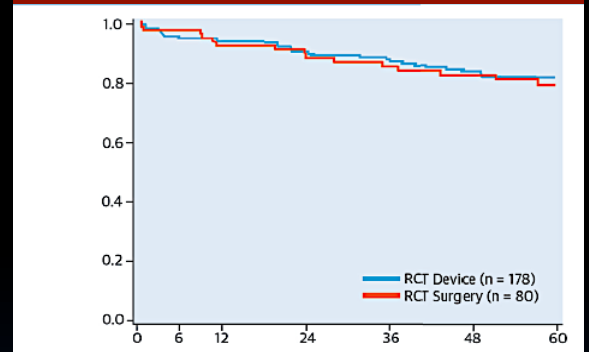
Randomized Comparison of Percutaneous Repair and Surgery for Mitral Regurgitation
- 5-year results of the **EVEREST II trial** -

Freedom from death, MV surgery or reoperation



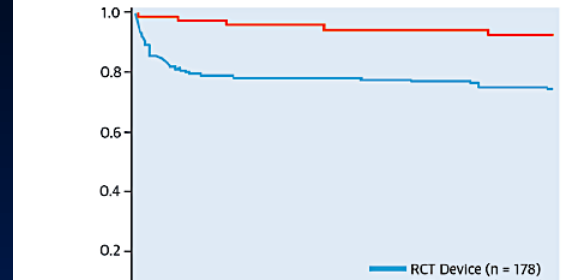
Patients At Risk				Months			
Device Group	178	136	128	117	109	98	45
Control Group	80	75	69	63	54	49	21

Freedom from death



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

Freedom from MV surgery or reoperation



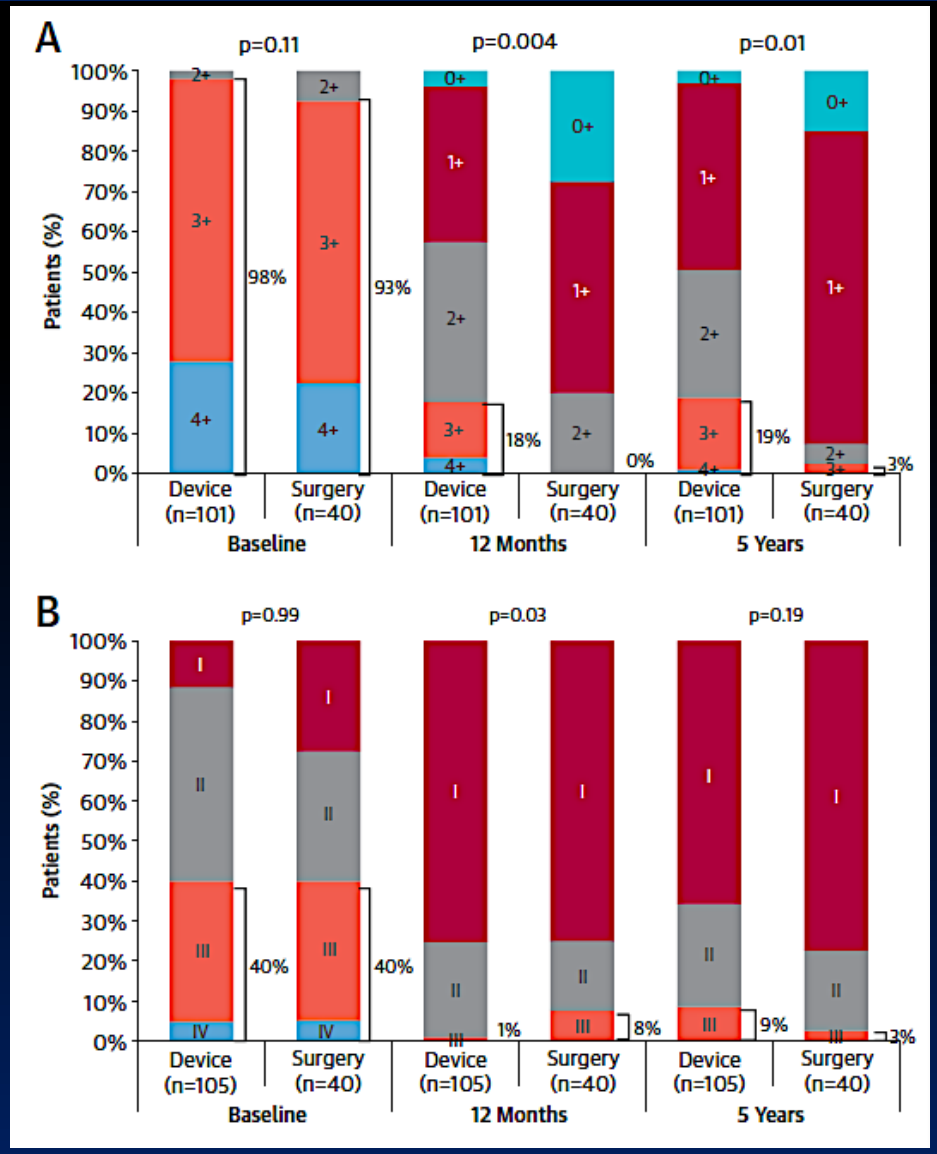
Patients At Risk				Months			
Device Group	178	136	128	117	109	98	45
Control Group	80	75	69	63	54	49	21

Feldman T, et al. J Am Coll Cardiol 2015; 66: 2744-2854

Randomized Comparison of Percutaneous Repair and Surgery for Mitral Regurgitation
- 5-year results of the **EVEREST II trial** -

Severity of MR and Heart Failure Symptoms Post-Treatment

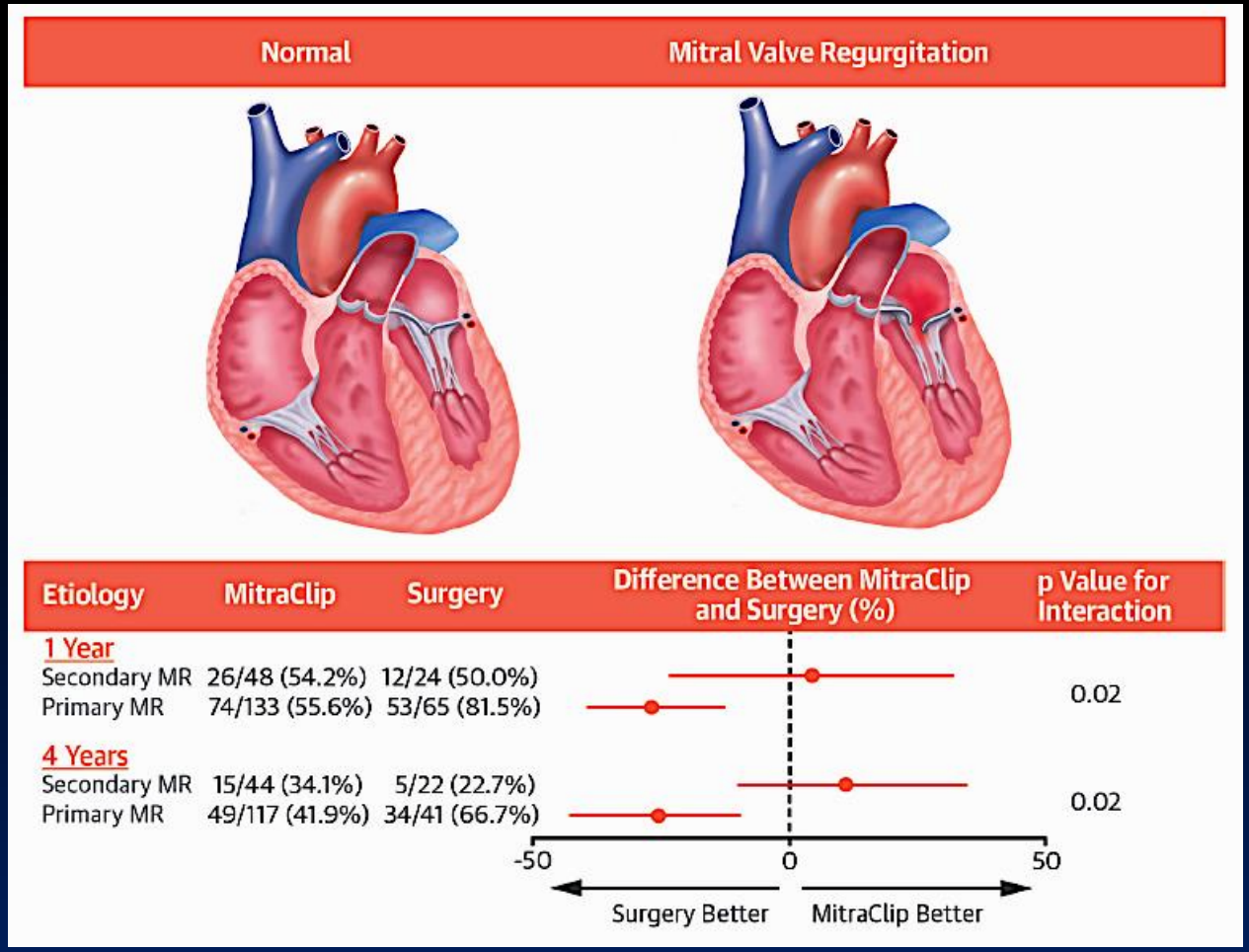
For patients who survived to 5 years comparisons are seen for:
(A) *echocardiographic severity of residual MR* in 101 of 40 patients in the device and surgery arms, respectively, and
(B) *New York Heart Association (NYHA) functional class* in 105 and 40 patients in the device and surgery arms, respectively, MR= Mitral Regurgitation.



Feldman T, et al. J Am Coll Cardiol 2015; 66: 2744-2854

Randomized Comparison of Percutaneous Repair and Surgery for Mitral Regurgitation
- 5-year results of the **EVEREST II trial** -

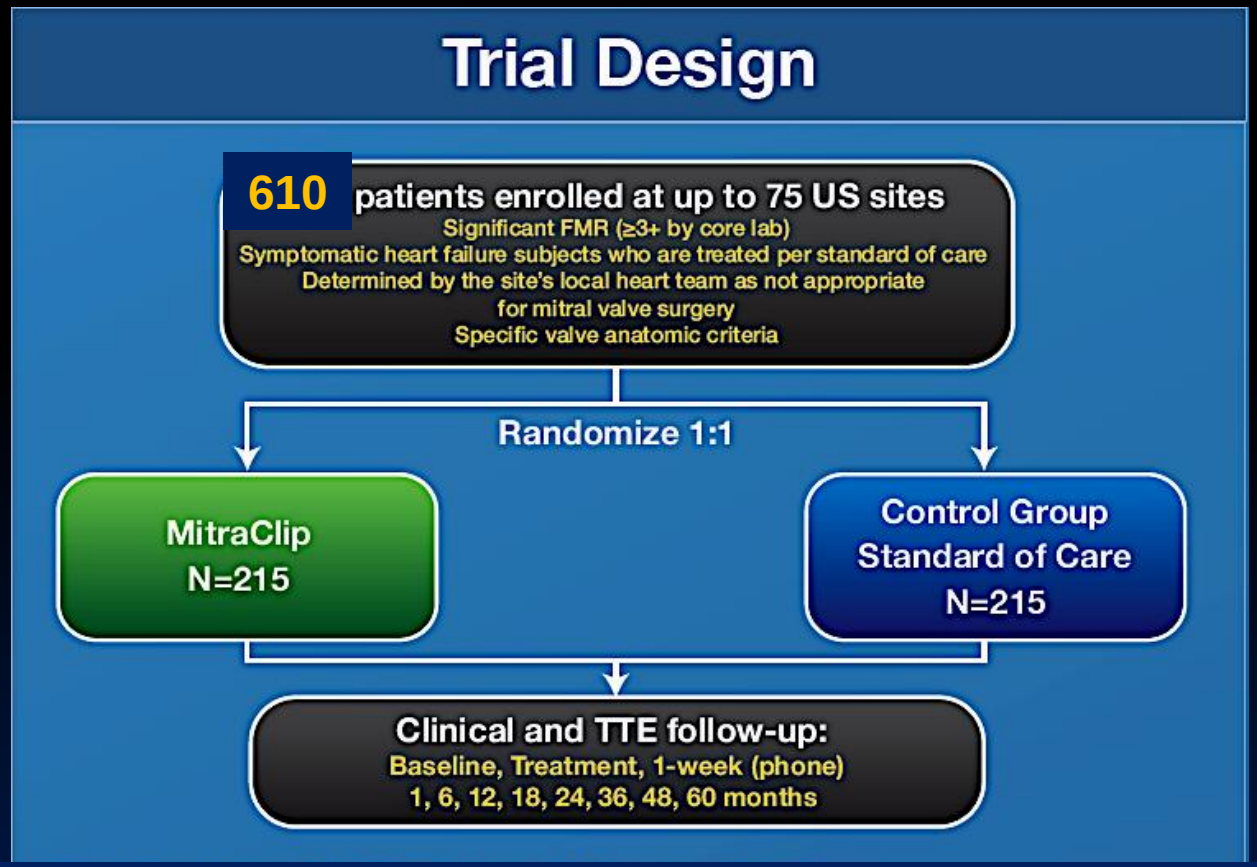
Secondary MR in heart failure: Interaction between the etiology of MR and the relative success of MV surgery and MitraClip in the Randomized EVEREST II Trial



Asgar A, et al. J Am Coll Cardiol 2015; 65: 1231-1248

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

- The COAPT Trial -



- Study start date: Aug 2012
- Estimated primary completion date: Jul 2018 (final data collection date for primary outcome measures)

http://clinicaltrials.gov/ct2/show/NCT01626079

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

- The COAPT Trial -

Primary Endpoints:

Primary effectiveness (minimum 1-year follow-up on all patients)

- Recurrent heart failure hospitalizations

Primary Safety (1-year)

- Composite of single leaflet device attachment (SLDA), device embolization, endocarditis requiring surgery, echocardiography core laboratory confirmed mitral stenosis requiring surgery, any device related complications requiring non-elective cardiovascular surgery at 12 months.

Secondary Endpoints:

Secondary effectiveness

- MR severity at 12 months
- Changes in 6MWD at 12 months
- Change in QoL score (KCCQ) at 12 months
- Change in LVEDV at 12 months
- Reduction in NYHA functional class I/II at 12 months
- Hierarchical composite of death and recurrent HF hospitalizations
- Recurrent hospitalizations (all cause)

Secondary Safety

- Composite of death (all-cause), stroke, MI, non-elective CV surgery device related complications in device group at 30 days

http://clinicaltrials.gov/ct2/show/NCT01626079

Comparison of Ongoing Randomized Trials of the MitraClip in Patients With Heart Failure and Secondary Mitral Regurgitation

	COAPT	RESHAPE-HF	MITRA-FR
Number of patients and sites	430 patients at 75 U.S. and Canadian sites	800 patients at 50 E.U. sites	288 patients at 18 French sites
Secondary MR grade (core laboratory verified)	≥3+ (EROA ≥30 mm^2 and/or Rvol >45 ml)	≥3+ (EROA ≥30 mm^2 and/or Rvol >45 ml)	Severe (EROA >20 mm^2 + Rvol >30 ml)
NYHA functional class	II, III, or ambulatory IV	III or ambulatory IV	II-IV
LVEF	≥20% to ≤50%	≥15% to ≤40%	≥15% to ≤40%
Surgical criteria	Not appropriate for mitral valve surgery (heart team)	None	None
Left ventricular volume entry criterion	LV end-systolic dimension ≤70 mm	LV end-diastolic dimension ≥55 mm	None
Control arm	Guideline-directed medical therapy (+CRT, if indicated)	Guideline-directed medical therapy (+CRT, if indicated)	Guideline-directed medical therapy (+CRT, if indicated)
Primary efficacy endpoint (superiority)	Heart failure rehospitalizations at 1 yr	Death or heart failure hospitalization at 1 yr	Death or recurrent heart failure hospitalization at 1 yr
Primary safety endpoint (noninferiority)	The composite of: SLDA; device embolization; endocarditis requiring surgery; echocardiography core laboratory-confirmed mitral stenosis requiring surgery; LVAD implant; heart transplant; or any device-related complications requiring nonelective cardiovascular surgery at 12 months	None	None
Health economics	Assessed	Assessed	None
Follow-up, yrs	5	2	2

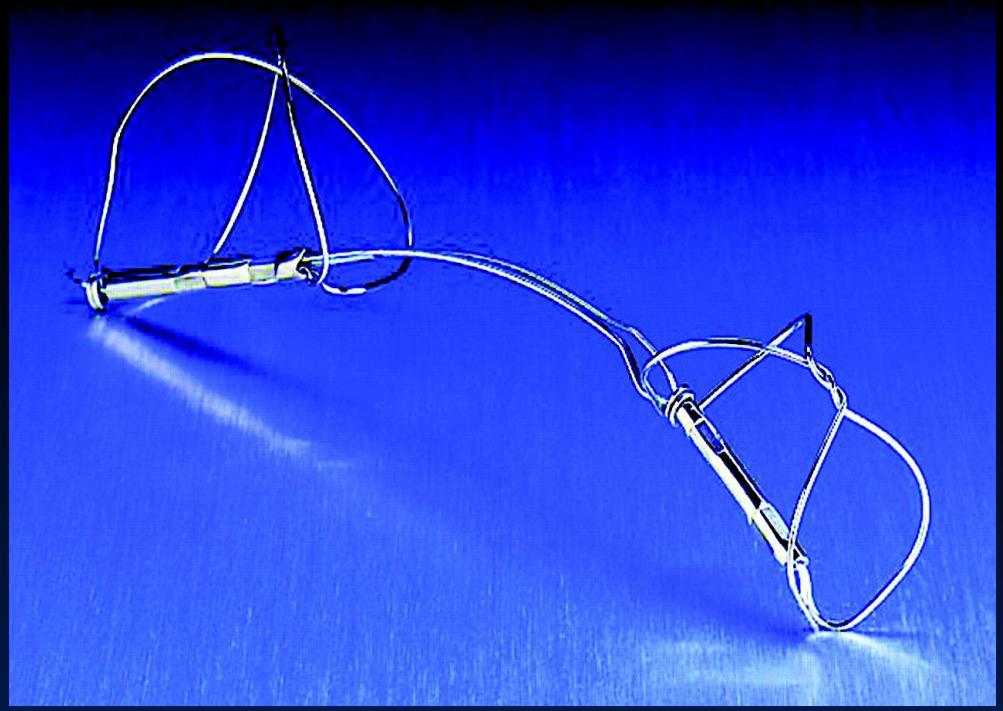
Asgar A, et al. J Am Coll Cardiol 2015; 65: 1231-1248

Transcatheter Mitral Valve Repair

- Indirect Annuloplasty -

Carillon® Mitral Countour System®

(Cardiac Dimensions Inc., Kirkland, WA, USA)



>600 implants worldwide

Percutaneous Mitral Annuloplasty for Functional MR

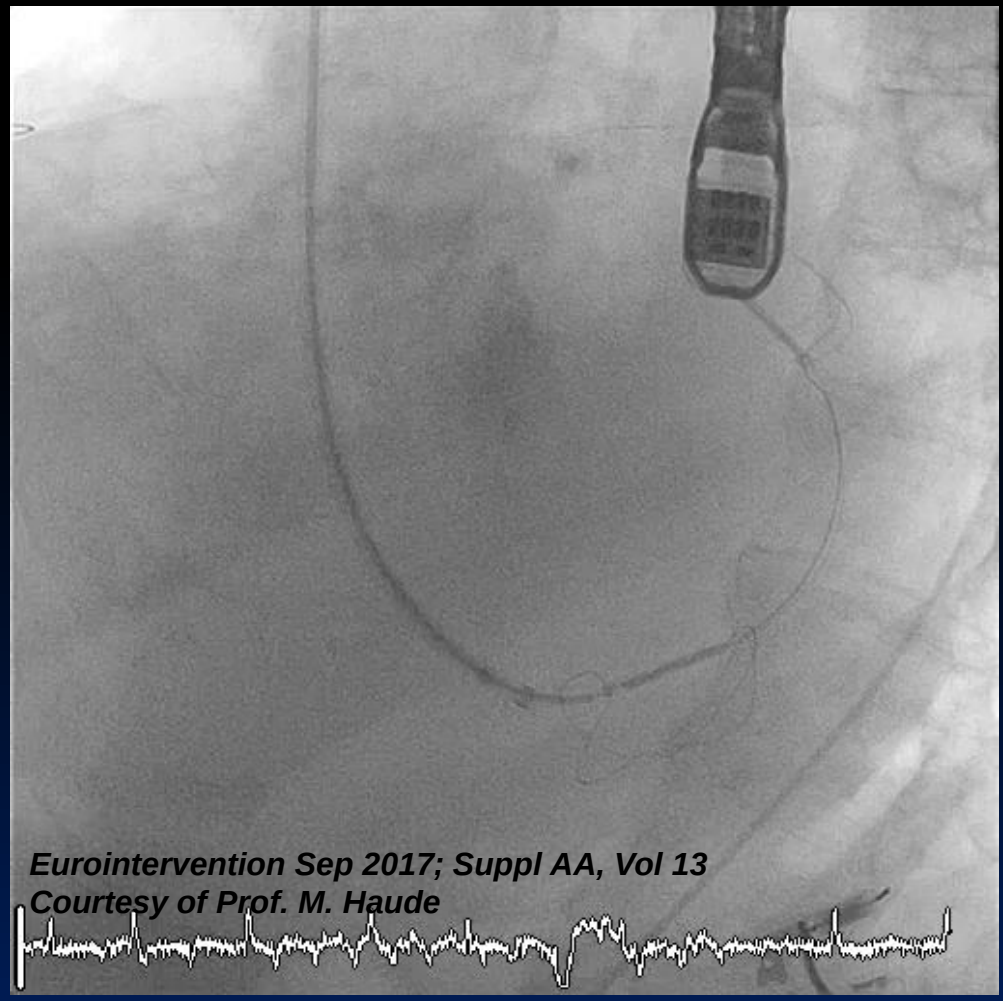
- Results of the CARILLON Mitral Annuloplasty Device European Union (**AMADEUS**) Study -

Primary objective

- Evaluate the safety of deploying the CARILLON implant in patients with FMR

Secondary objective

- Assessment of long-term (6 month) safety after the procedure
- Assessment of FMR reduction (quantitative and semi-quantitative evaluation by echocardiography)
- Assessment of clinical efficacy through changes in NYHA functional class, exercise tolerance and quality of life

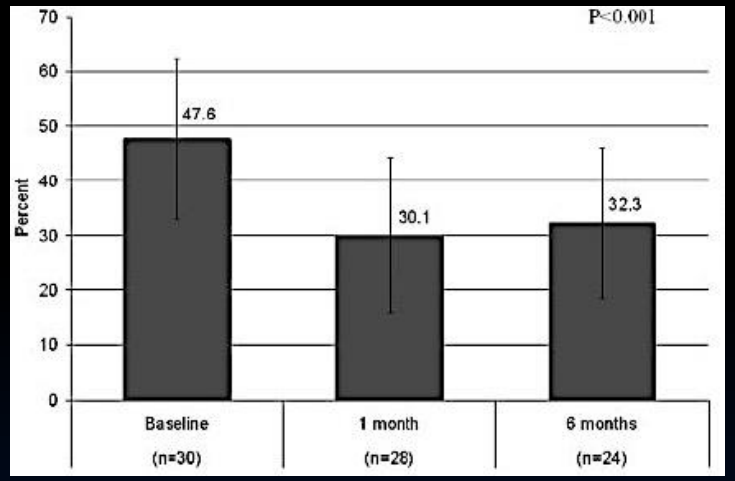


Eurointervention Sep 2017; Suppl AA, Vol 13
Courtesy of Prof. M. Haude

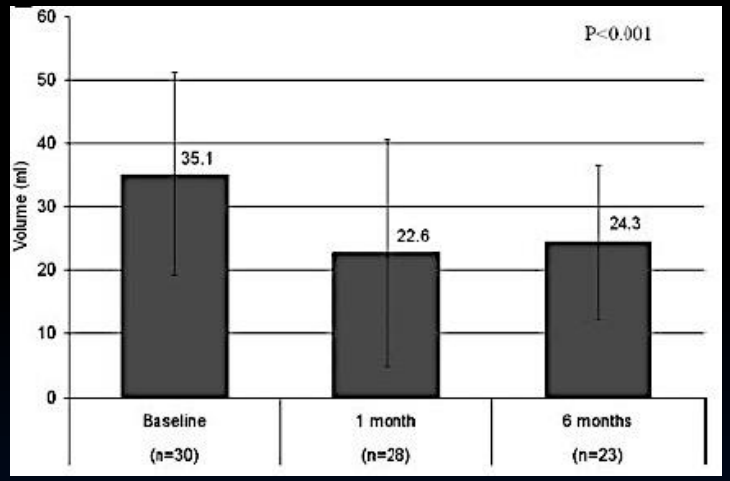
AMADEUS Study

- Effect of the CARILLON device implantation on the severity of mitral regurgitation -

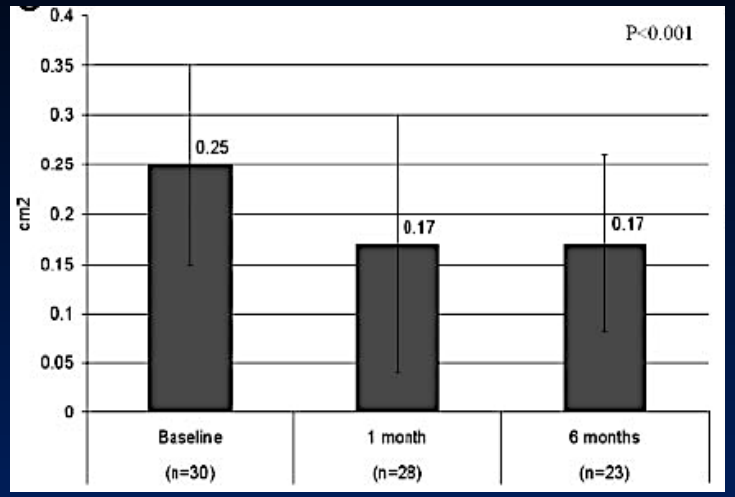
Mitral regurgitant JA/LA area ratio



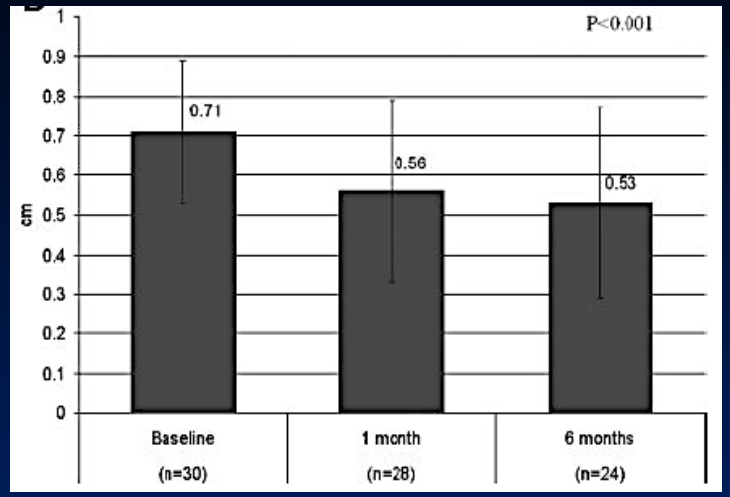
Regurgitant Volume



Effective regurgitant orifice area



Vena contracta

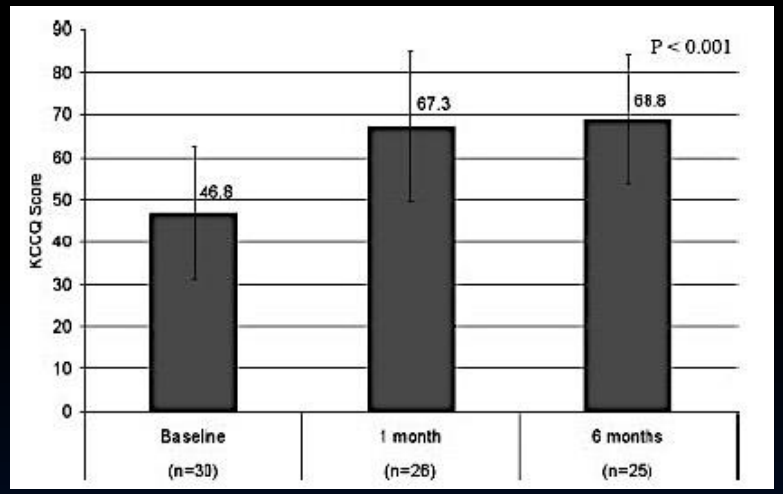


Schofer J, et al. Circulation 2009; 120: 326-333

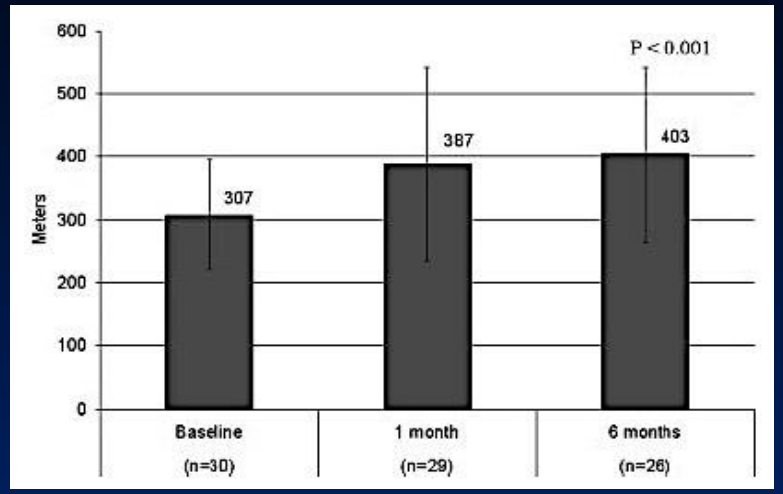
AMADEUS Study

- Effect of the CARILLON device implantation on the severity of mitral regurgitation -

Changes in KCCQ score



Changes in the 6 min walk distance



Changes in NYHA classification

	Baseline (n=30) (n/N)	At 1 month (n=29) (n/N)	At 6 months (n=26) (n/N)	P
NYHA class				<0.001
I	0 (0/30)	17 (5/29)	36 (9/25)	
II	20 (6/30)	62 (18/29)	52 (13/25)	
III	73 (22/30)	17 (5/29)	12 (3/25)	
IV	7 (2/30)	3 (1/29)	0 (0/25)	

Schofer J, et al. Circulation 2009; 120: 326-333

AMADEUS Study

- Effect of the CARILLON device implantation LV remodeling -

Hemodynamic changes for 30 implanted patients

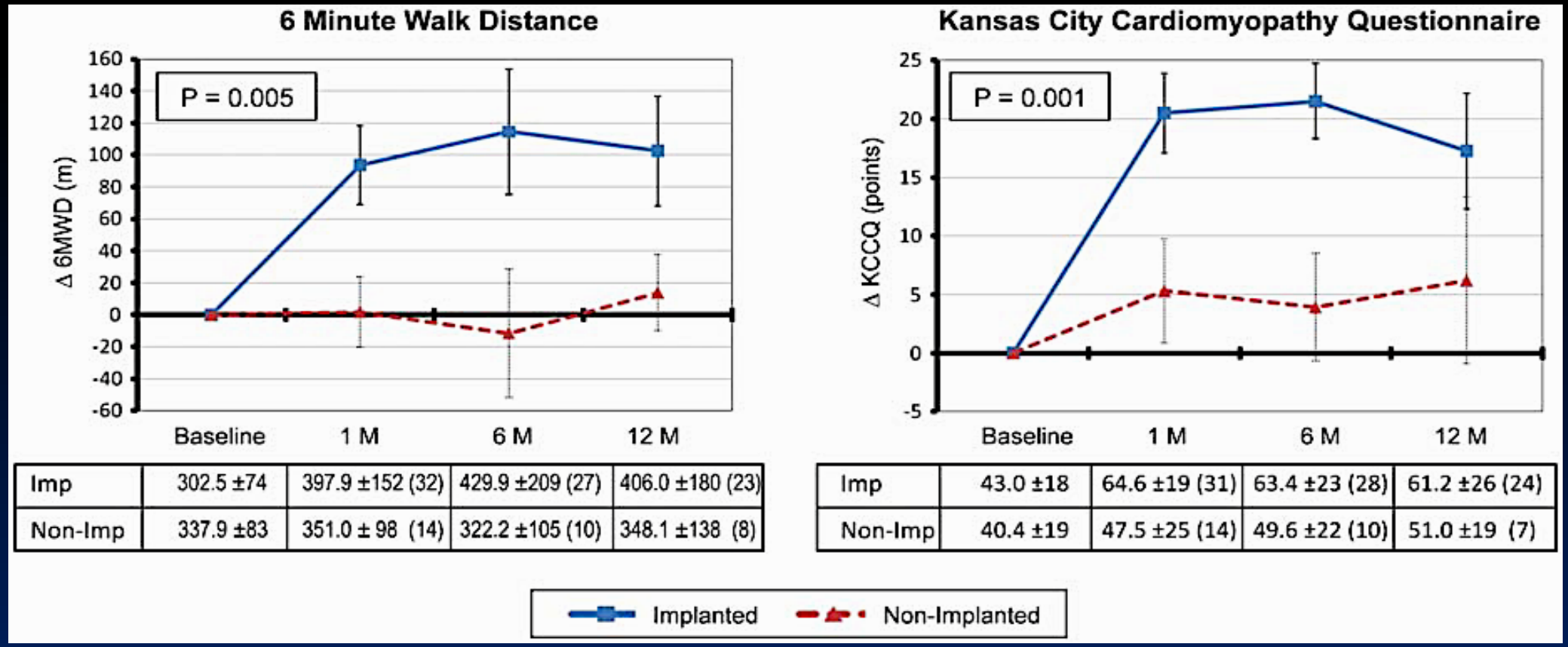
Parameter	Baseline (n=30)	At 1 mo (n=28)	At 6 mo (n=24)	*P*
LVEDD, cm	6.7±0.8	6.7±0.8	6.6±0.7	0.92
LVEDV, mL	217±63	204±57	192±46	0.20
LVEF, %	29.8±8	30.7±8	30.8±10	0.54
Mitral annular diameter, cm	4.20±0.4	3.81±0.4	3.78±0.5	<0.001

Schofer J, et al. Circulation 2009; 120: 326-333

Treatment of functional MR by percutaneous annuloplasty

The TITAN Study

Comparison of clinical outcome measures between implanted (n=36) and non-implanted (n=17) patients assessed by 6 MWD and KCCQ



Imp	302.5 ±74	397.9 ±152 (32)	429.9 ±209 (27)	406.0 ±180 (23)
Non-Imp	337.9 ±83	351.0 ± 98 (14)	322.2 ±105 (10)	348.1 ±138 (8)

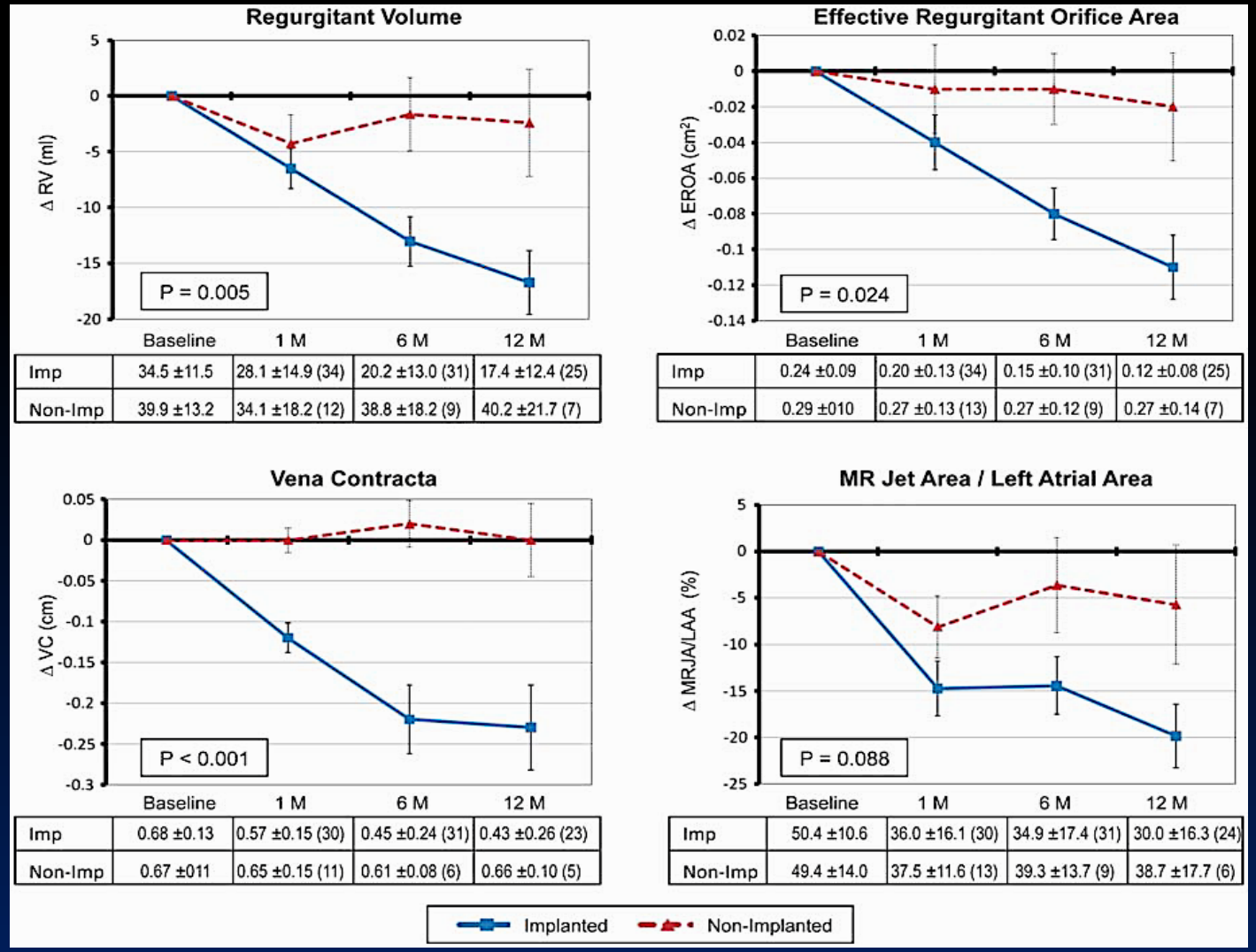
Imp	43.0 ±18	64.6 ±19 (31)	63.4 ±23 (28)	61.2 ±26 (24)
Non-Imp	40.4 ±19	47.5 ±25 (14)	49.6 ±22 (10)	51.0 ±19 (7)

Siminiak T, et al. Eur J Heart Fail 2012; 14: 931-938

The TITAN Study

- Echocardiographic Outcomes -

Echocardiographic changes in functional **MR severity** between implanted (n=36) and non-implanted (n=17) patients



Regurgitant Volume	Baseline	1 M	6 M	12 M
Imp	34.5 ±11.5	28.1 ±14.9 (34)	20.2 ±13.0 (31)	17.4 ±12.4 (25)
Non-Imp	39.9 ±13.2	34.1 ±18.2 (12)	38.8 ±18.2 (9)	40.2 ±21.7 (7)

Effective Regurgitant Orifice Area	Baseline	1 M	6 M	12 M
Imp	0.24 ±0.09	0.20 ±0.13 (34)	0.15 ±0.10 (31)	0.12 ±0.08 (25)
Non-Imp	0.29 ±010	0.27 ±0.13 (13)	0.27 ±0.12 (9)	0.27 ±0.14 (7)

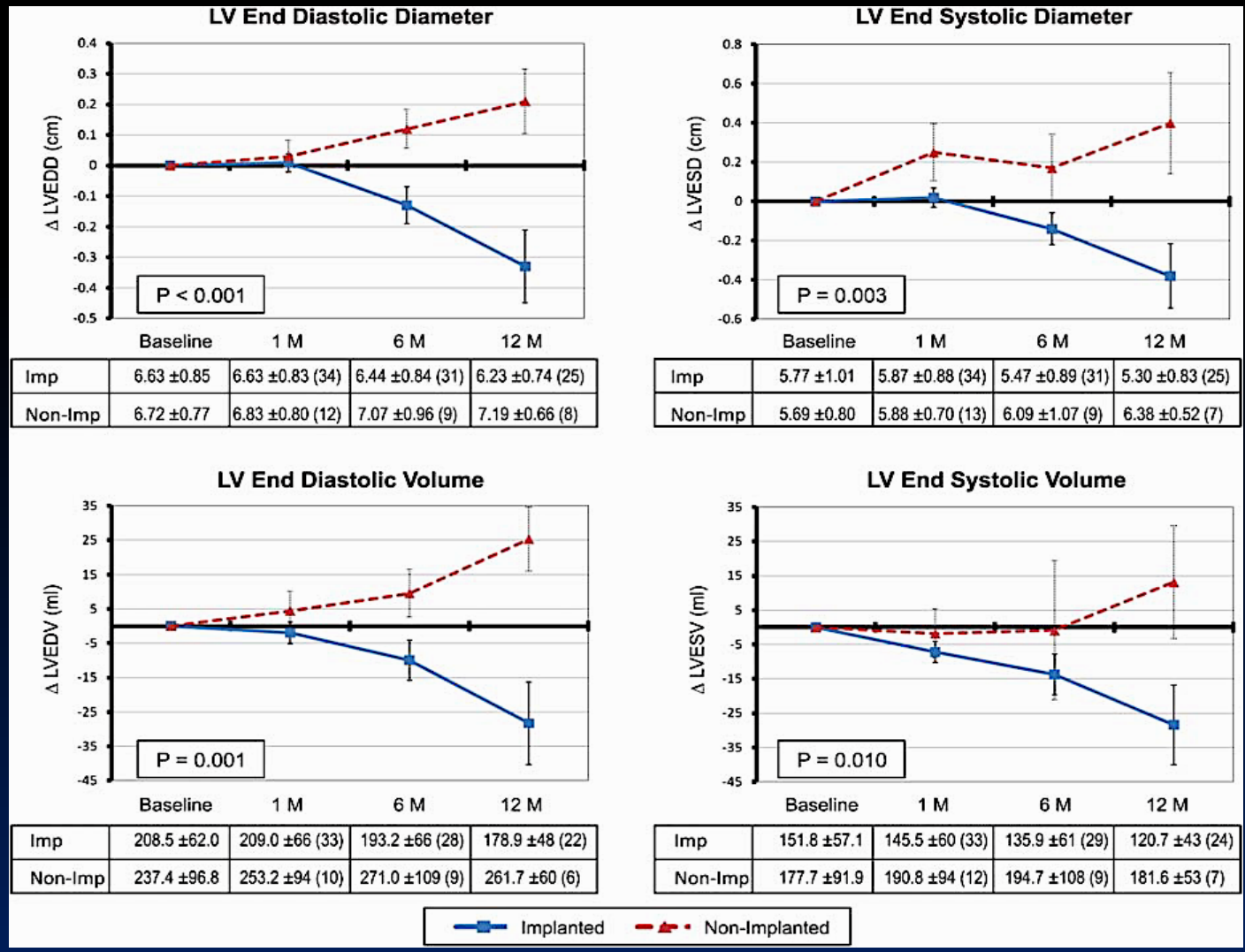
Vena Contracta	Baseline	1 M	6 M	12 M
Imp	0.68 ±0.13	0.57 ±0.15 (30)	0.45 ±0.24 (31)	0.43 ±0.26 (23)
Non-Imp	0.67 ±011	0.65 ±0.15 (11)	0.61 ±0.08 (6)	0.66 ±0.10 (5)

MR Jet Area / Left Atrial Area	Baseline	1 M	6 M	12 M
Imp	50.4 ±10.6	36.0 ±16.1 (30)	34.9 ±17.4 (31)	30.0 ±16.3 (24)
Non-Imp	49.4 ±14.0	37.5 ±11.6 (13)	39.3 ±13.7 (9)	38.7 ±17.7 (6)

Siminiak T, et al. Eur J Heart Fail 2012; 14: 931-938

The TITAN Study
- Echocardiographic Outcomes -

Echocardiographic changes in **LV dimensions** between implanted (n=36) and non-implanted (n=17) patients

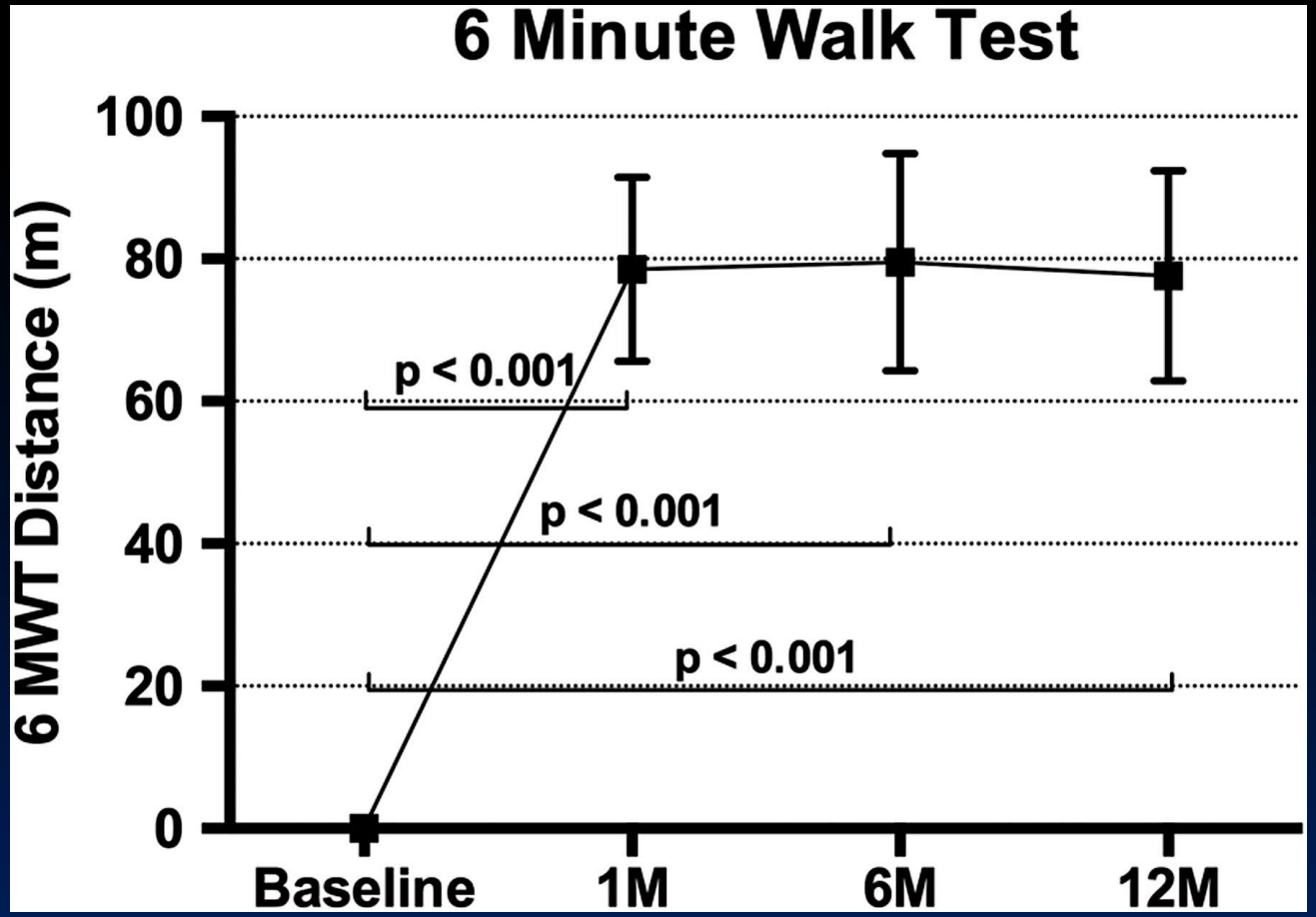


Siminiak T, et al. Eur J Heart Fail 2012; 14: 931-938

The TITAN II Trial (mXE2)

- Echocardiographic Outcomes -

6MWT results showing improvement from baseline at 1, 6 and 12 months in patients receiving an implant (mean ± SE of mean)

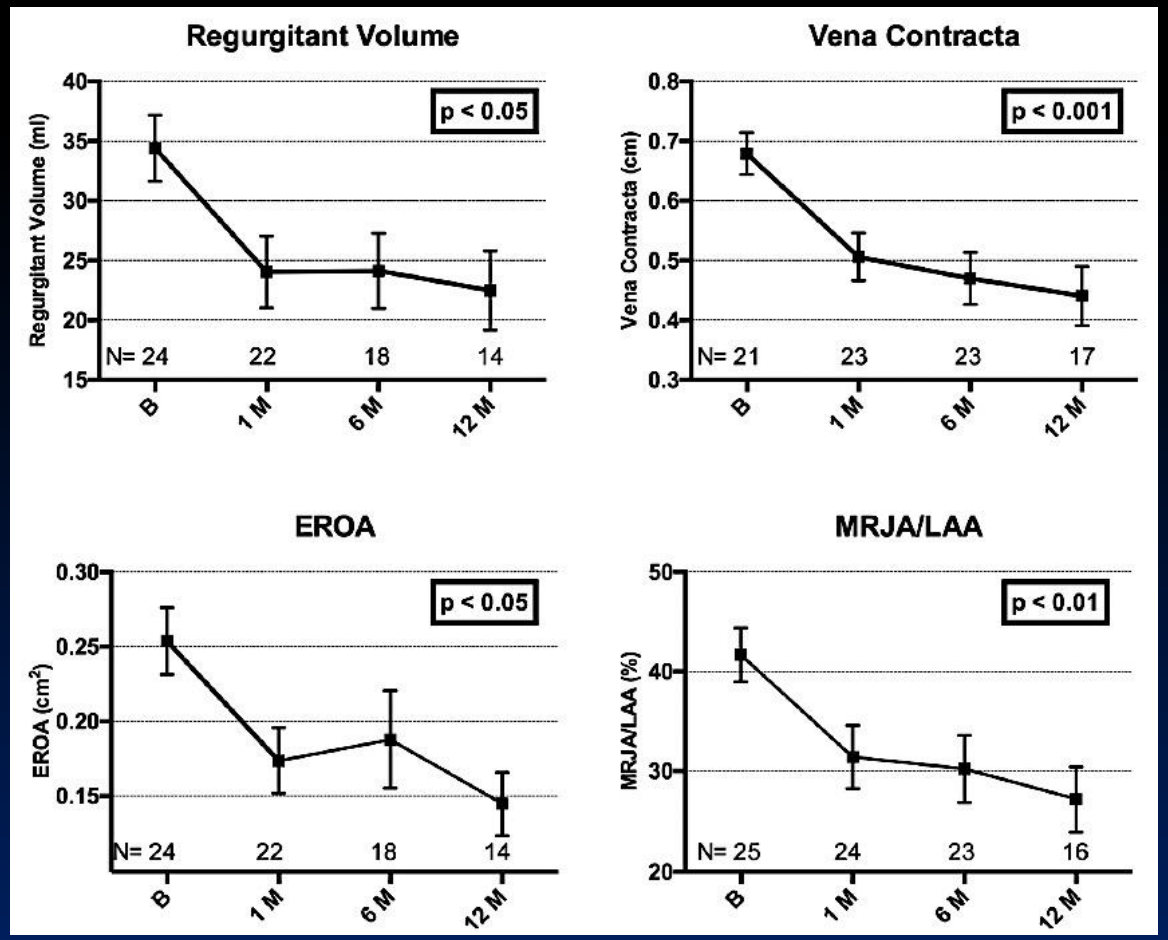


Lipiecki J, et al. Open Heart 2016; 3: e000411

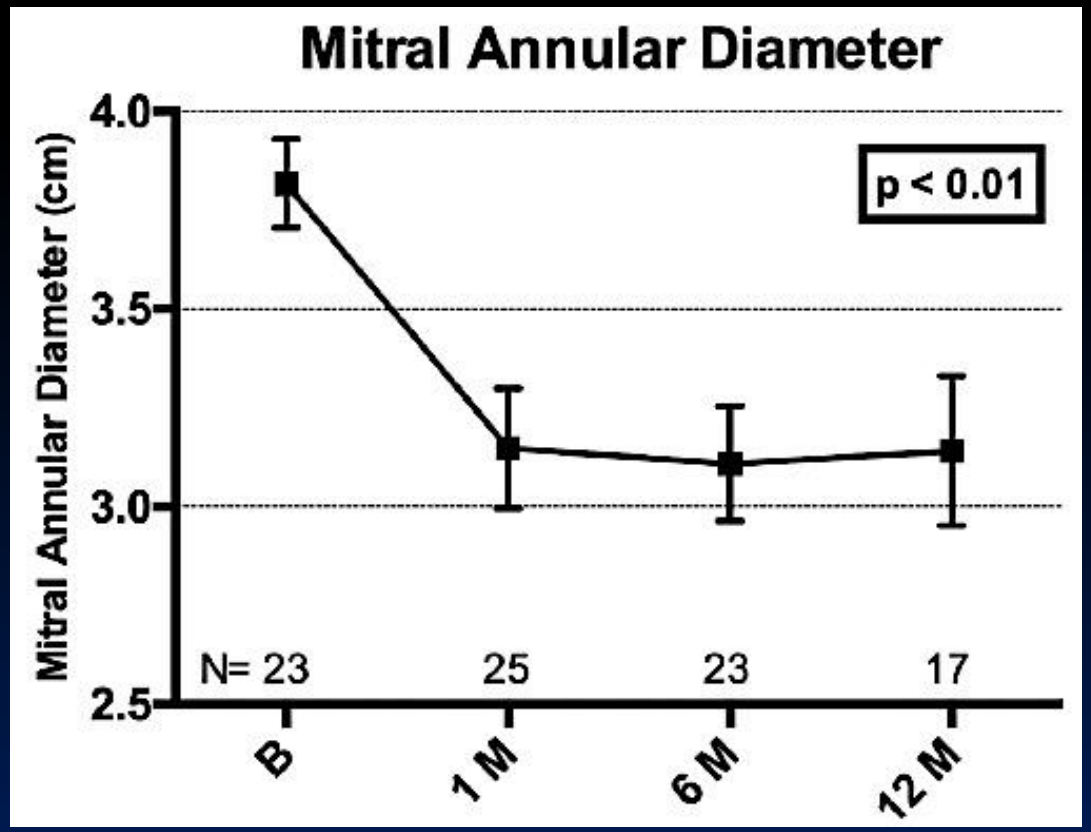
The TITAN II Trial (mXE2)

- Echocardiographic Outcomes -

Quantitative parameters of mitral regurgitation demonstrating improvements from baseline (mean ± SE of mean)



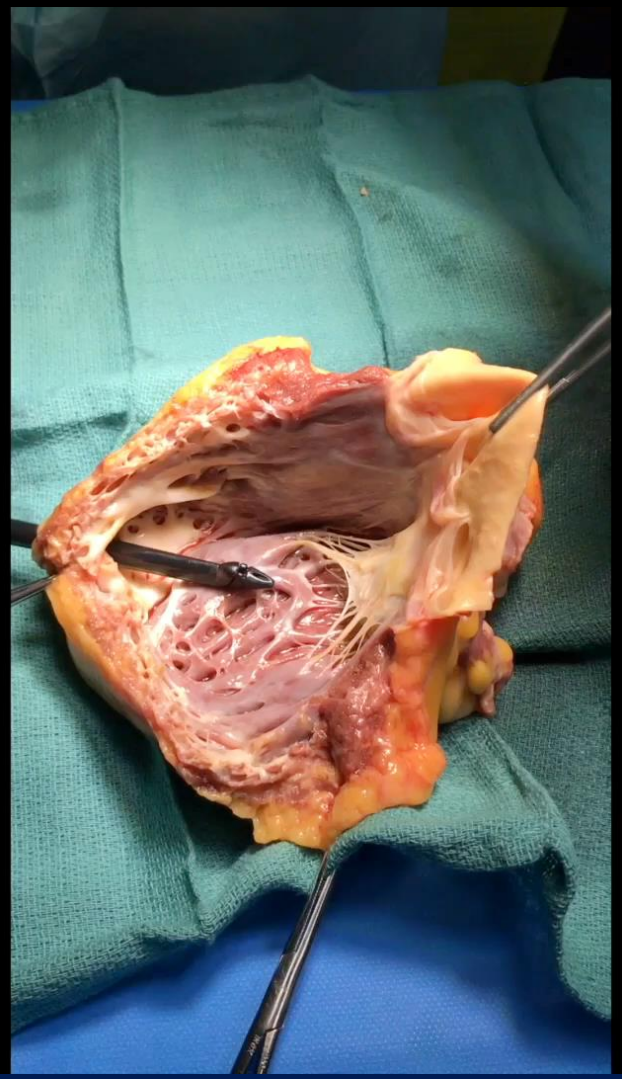
Plot of mitral annular (A-P) diameter at1, 6, and 12 months, showing mean ± SE of mean



Lipiecki J, et al. Open Heart 2016; 3: e000411

Chordal Replacement

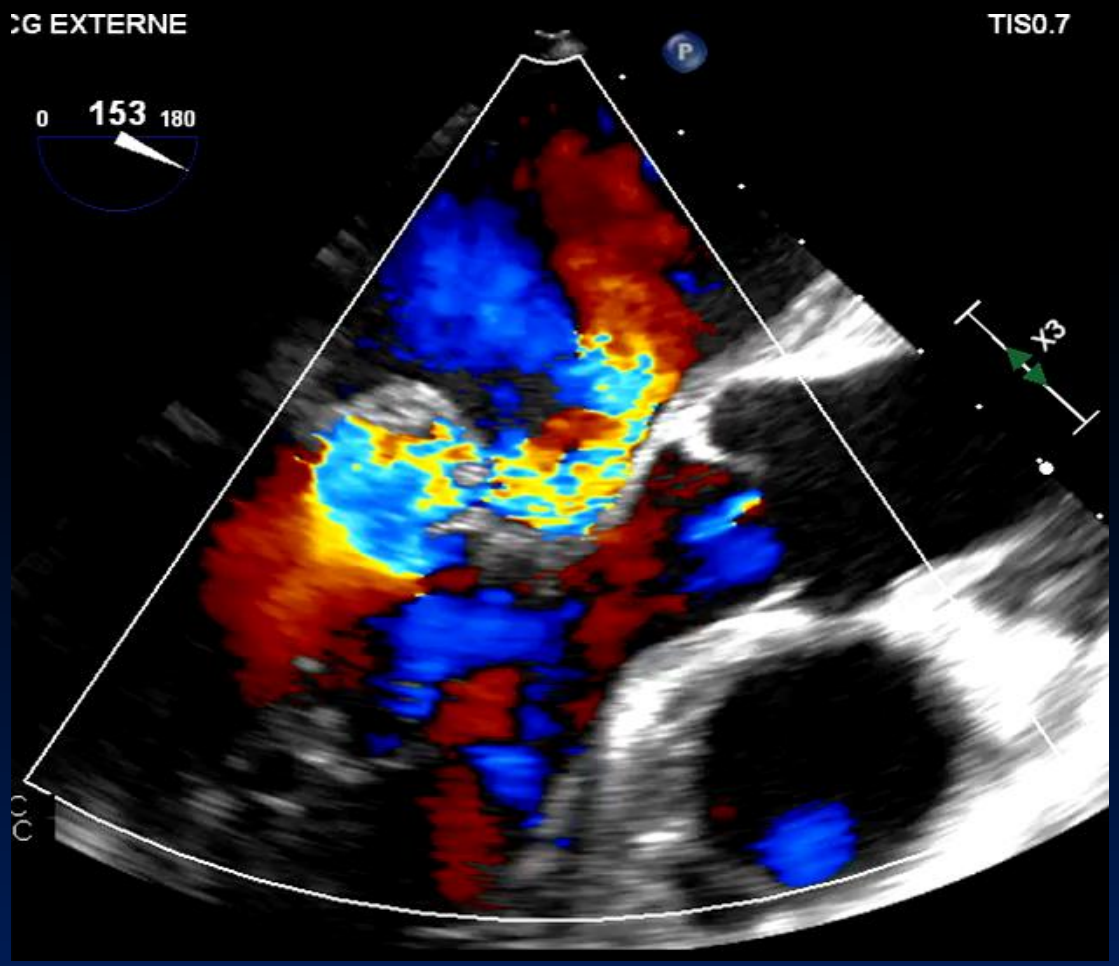
- NeoChord DS 1000 system -

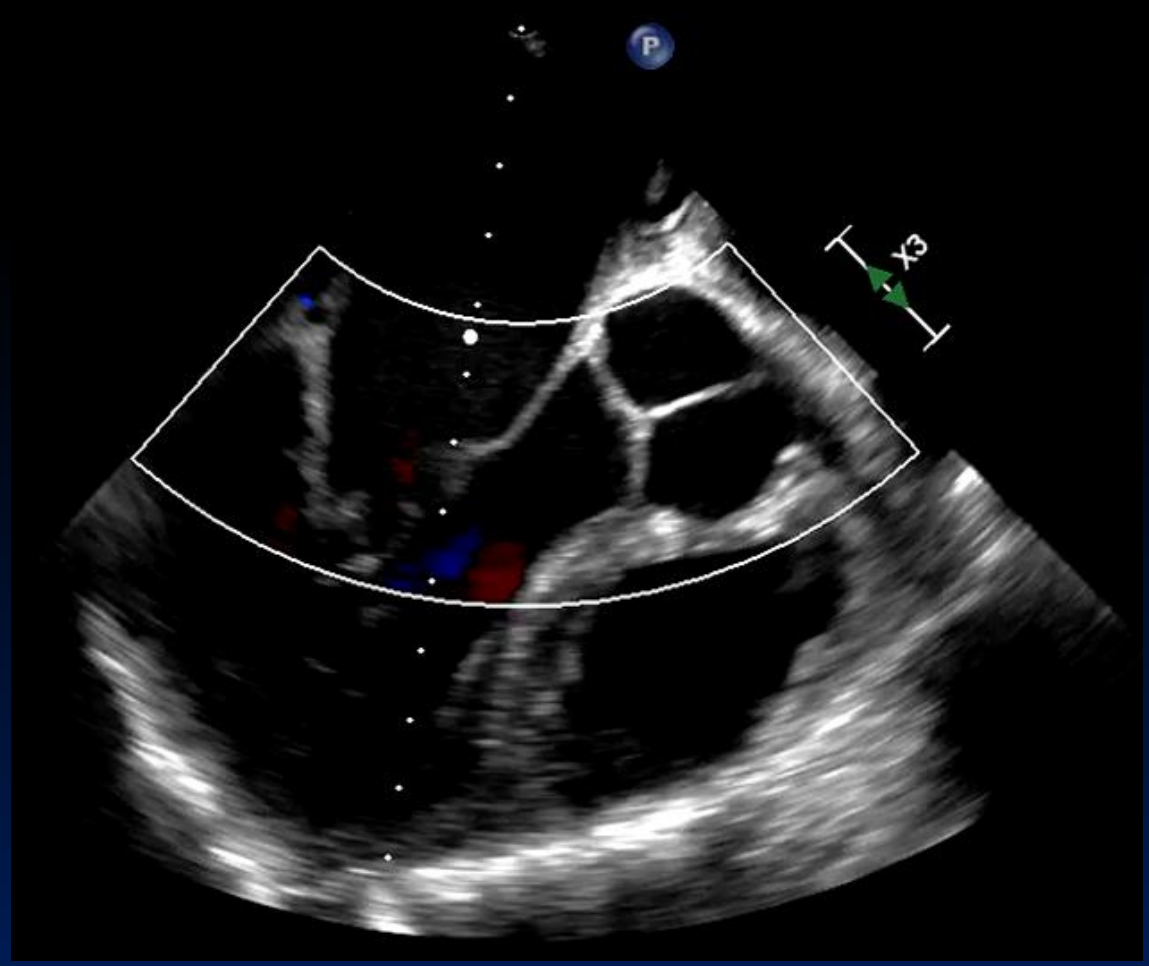


Vahanian A, et al. Eurointervention 2017; 13: AA22-AA30

Chordal Replacement

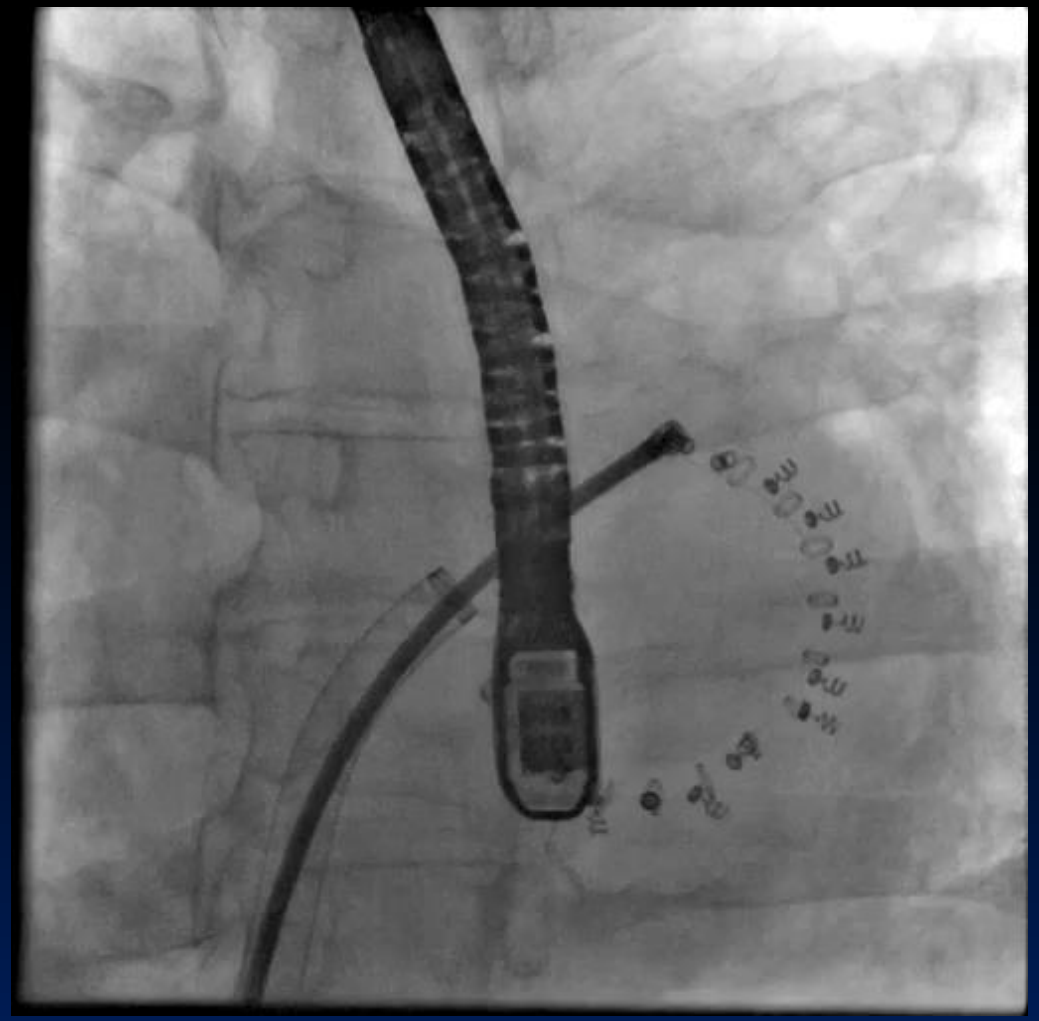
- NeoChord DS 1000 system -

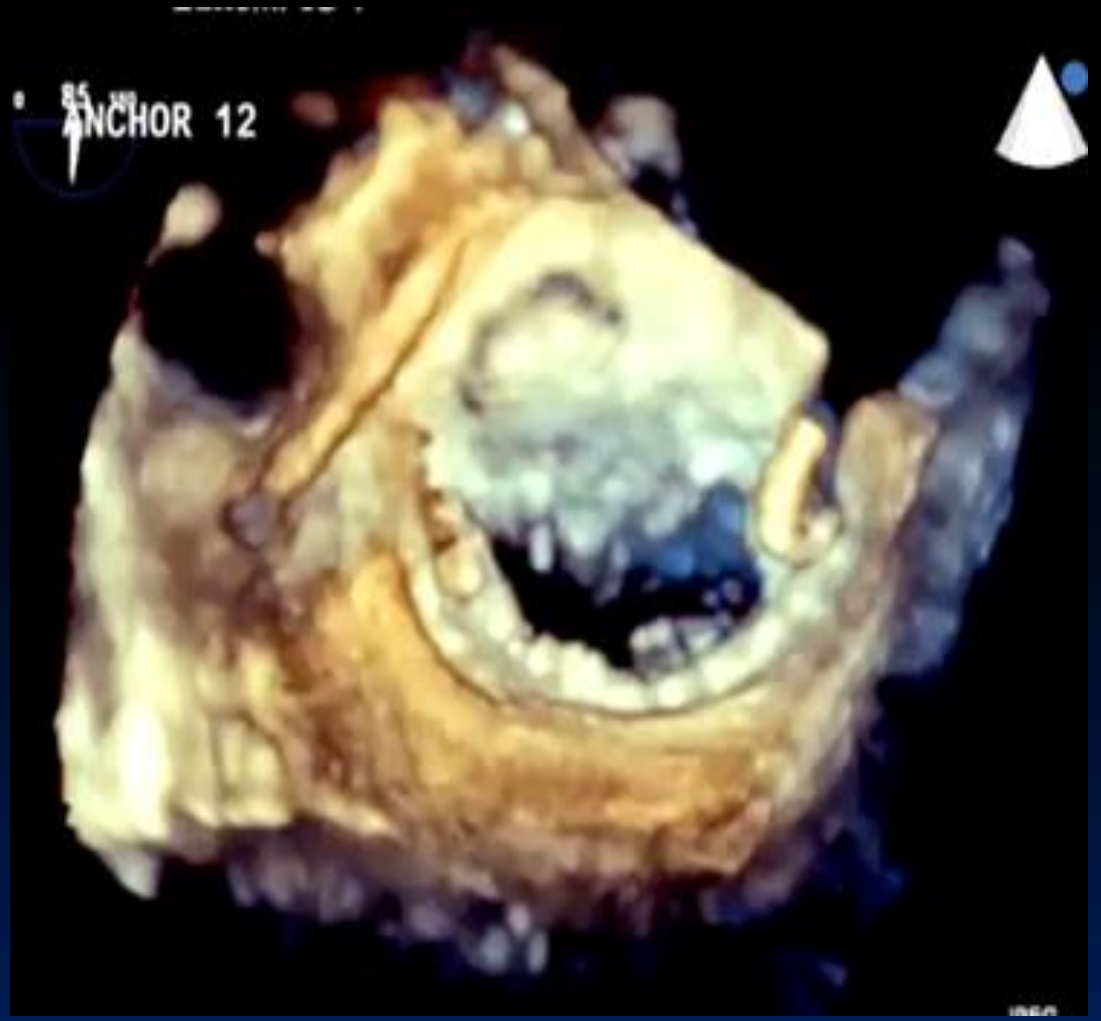




Vahanian A, et al. Eurointervention 2017; 13: AA22-AA30

Direct Annulplasty
- Cardioband -



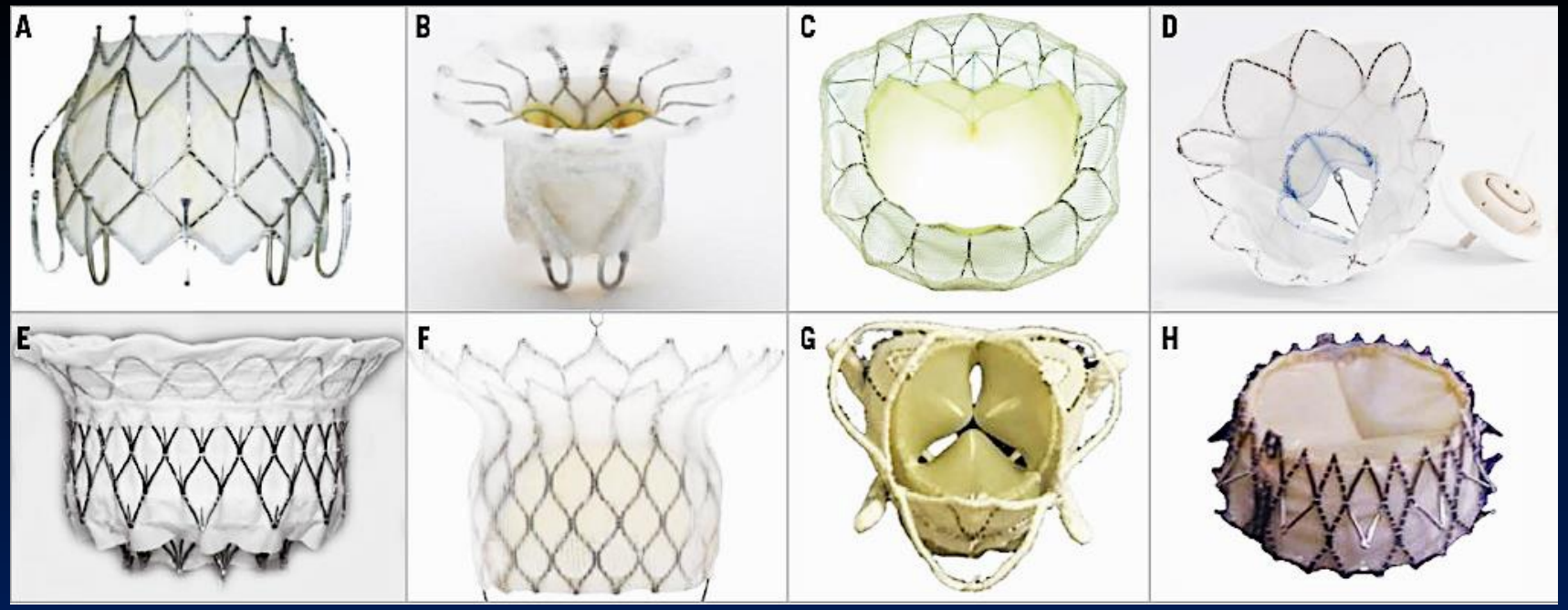


Vahanian A, et al. Eurointervention 2017; 13: AA22-AA30

Transcathter Mitral Valve Replacement

- Device Landscape and Stage of Development -

(A) CardiAQ valve system: Feasibility Trial
(B) FORTIS valve: on hold
(C) Tiara: Feasibility trial
(D) Tendyne Valve: feasibility trial
(E) Interpid (Medtronic): Feasibility trial
(F) HighLife: feasibility trial
(G) Caisson: preclinical trials underway
(H) Navi Mitral Valved Stent: preclinical trial



Patel A, et al. Eurointervention 2017; 13: AA31-AA39

Guidelines recommendations for catheter-based intervention for chronic, severe mitral regurgitation

2017 Focused update of the 2014 ACC/AHA guidelines on the management of valvular heart disease

Recommendation	COR	LOE
Transcatheter mitral valve repair may considered for severely symptomatic patients (NYHA class III to IV) with chronic severe **primary** MR who have favorable anatomy for repair procedure and a reasonable life expectancy but who have a **prohibitive surgical risk because of severe comorbidities and remain severely symptomatic despite optimal GDMT for heat failure**.	**IIb**	B
no recommendations for catheter-based mitral valve therapies in patients with chronic, severe, symptomatic secondary mitral regurgitation!!		

Guidelines recommendations for catheter-based intervention for chronic, severe mitral regurgitation

2017 ESC guidelines for the management of valvular heart disease

Recommendation	COR	LOE
Percutaneous edge-to-edge procedure may be considered in patients with symptomatic severe **primary** mitral regurgitation who fulfil the echocardiographic criteria for eligibility and are **judged inoperable or at high risk by the heart team, avoiding futility**	**IIb**	C
When revascularization is not indicated and surgical risk is not low, a percutaneous edge-to-edge procedure may be considered in patients with severe **secondary** mitral regurgitation and LVEF >30% who remain symptomatic despite GDMT (including CRT if indicated) and who have a suitable valve morphology by echocardiography avoiding futility	**IIb**	C
In patients with severe **secondary** mitral regurgitation and LVEF <30% who remain symptomatic despite GDMT (including CRT) and who have no option for revascularization, the heat team may consider percutaneous edge-to-edge procedure or valve surgery after careful evaluation for a ventricular assist device or heart transplantation according to individual patient characteristics	**IIb**	C

Contemporary Management of Chronic Severe Mitral Regurgitation

Hatim Al Lawati MD, FRCPC, FACC

Consultant | Interventional Cardiology

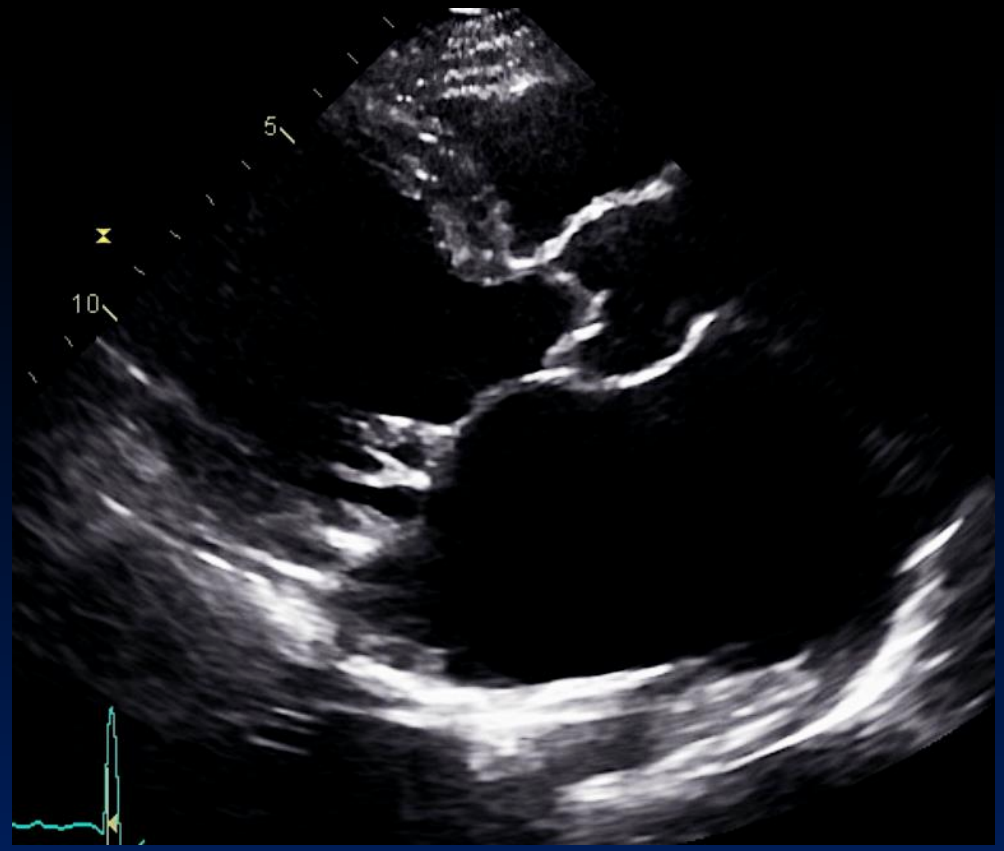
Sultan Qaboos University Hospital | Oman

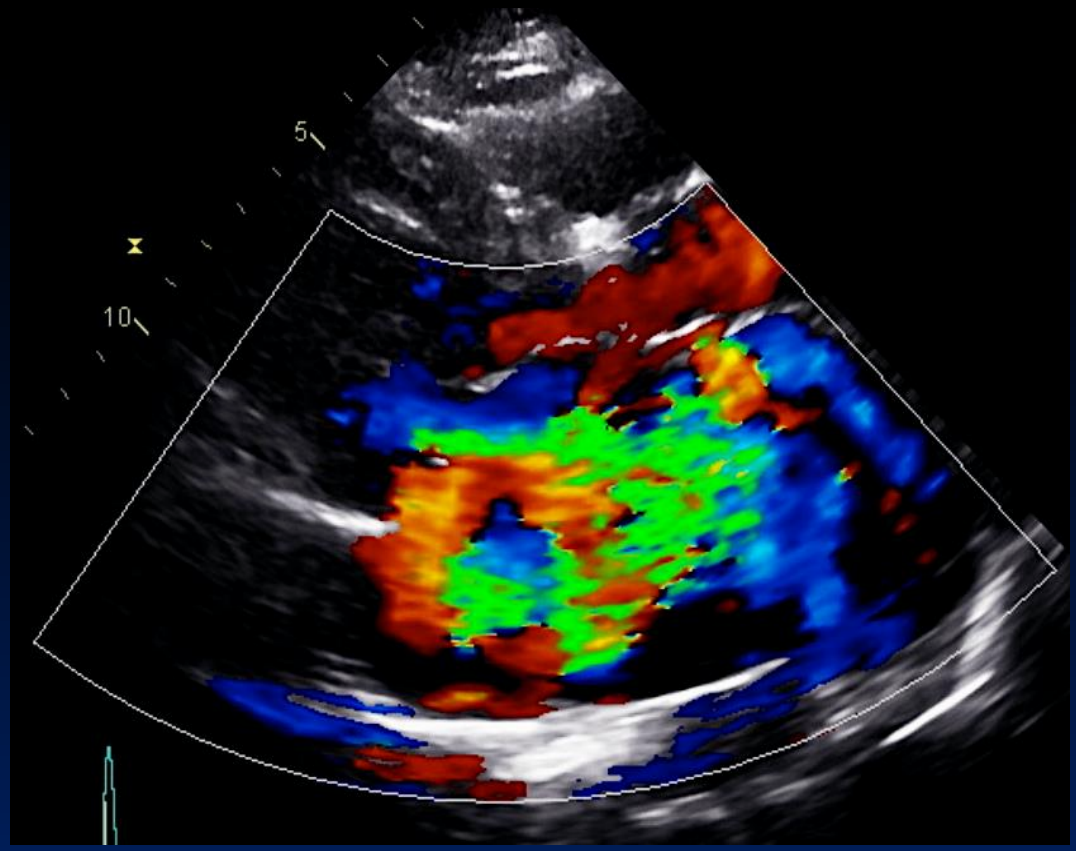
hatim.al.lawati@gmail.com

Additional Slides

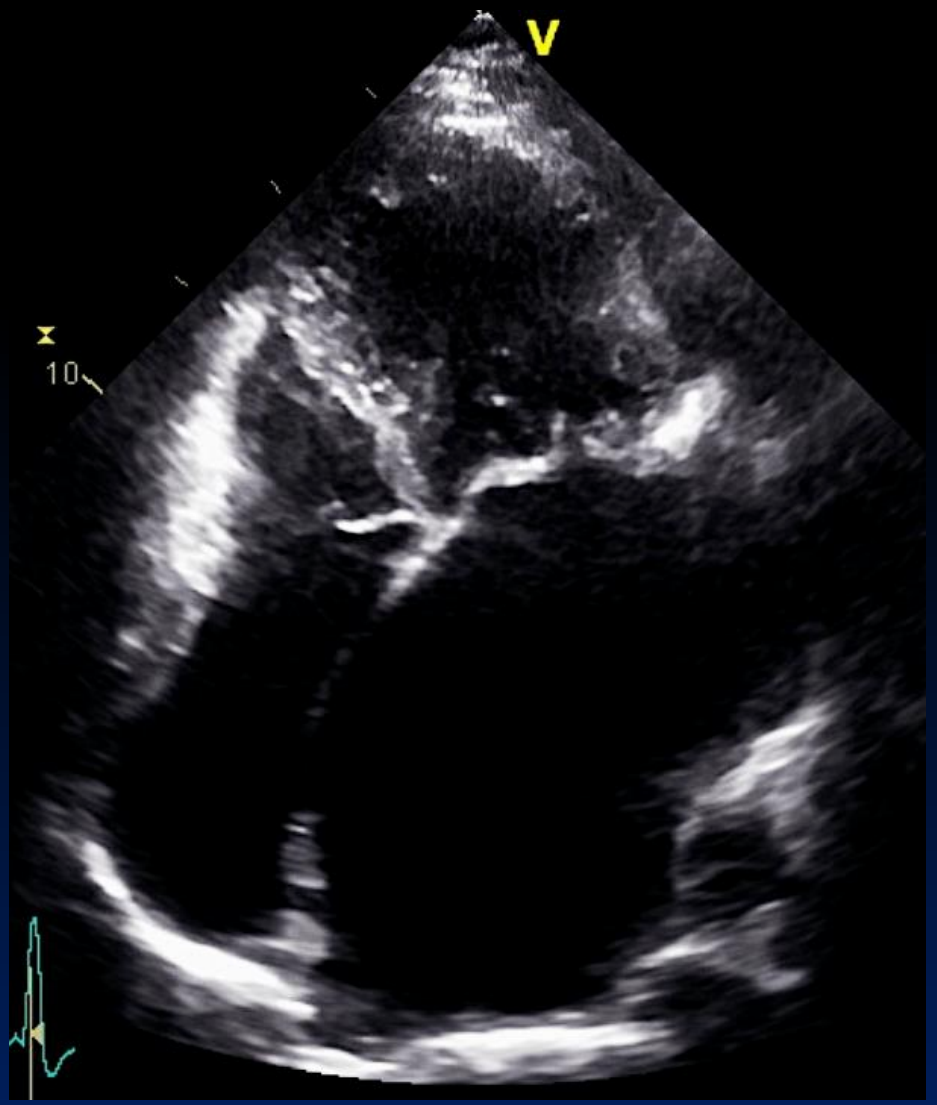
- Case (1) -

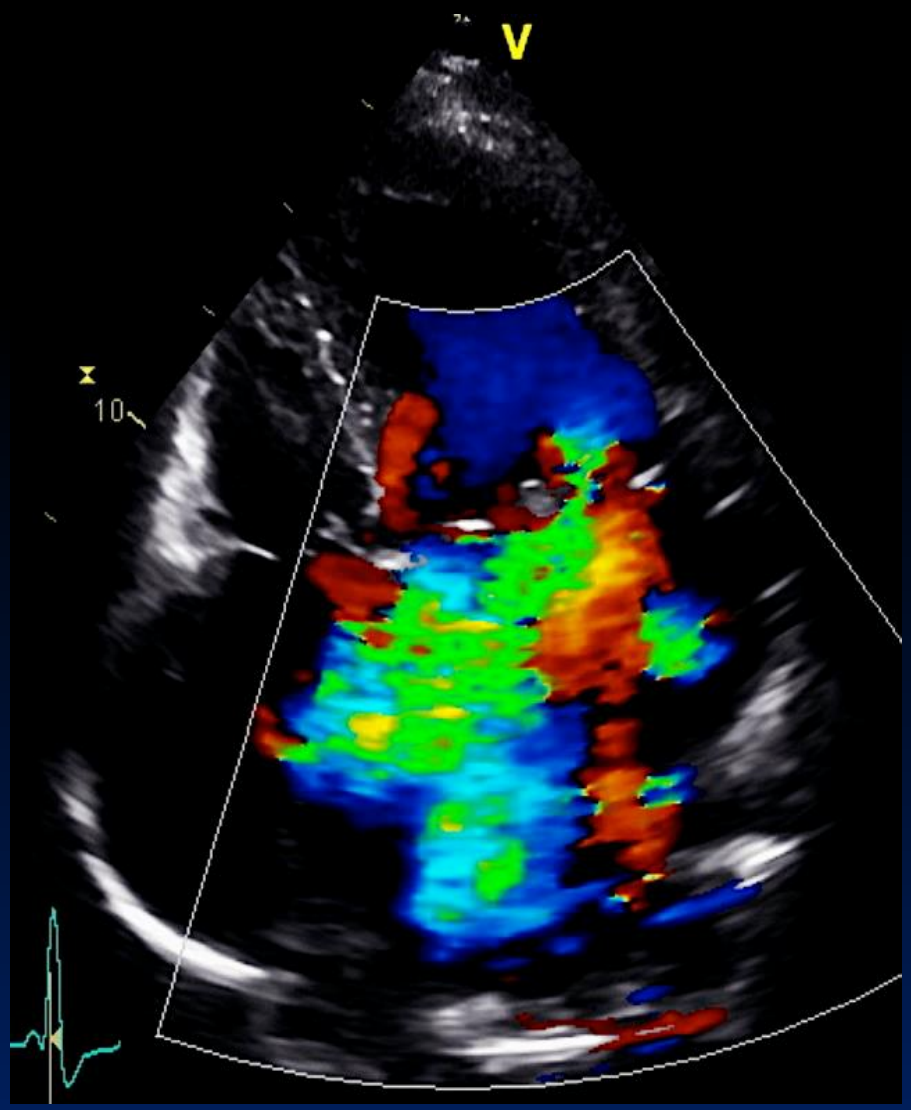
67-year-old female with hypertension, diabetes, chronic kidney disease (eGFR= 25 ml/min), permanent AF, prior ischemic stroke with residual right sided motor weakness, recurrent hospitalizations for decompensated HF, severe pulmonary hypertension (PASP ~65 mmHg on 2D transthoracic echocardiography)



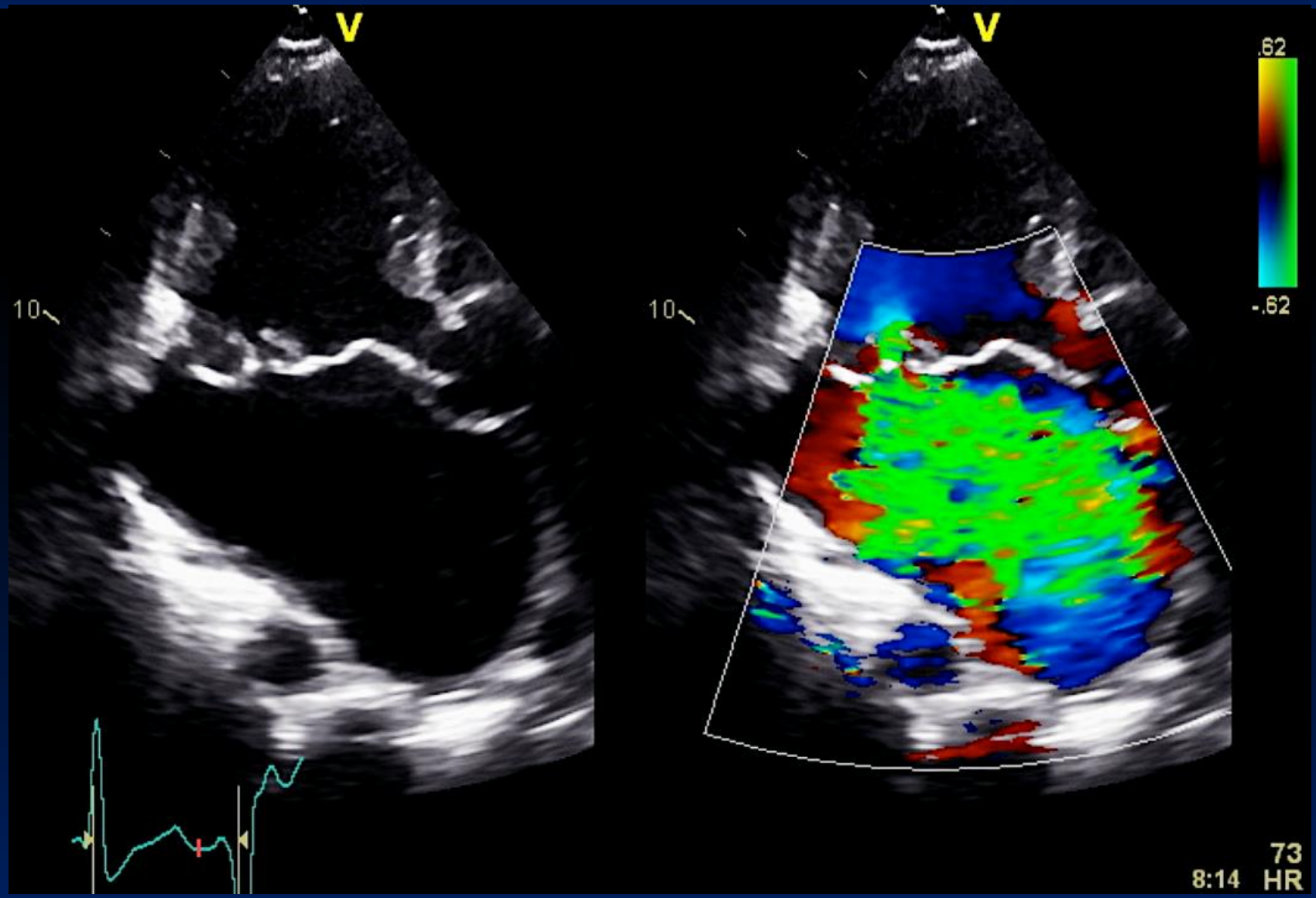


- Case (1) -

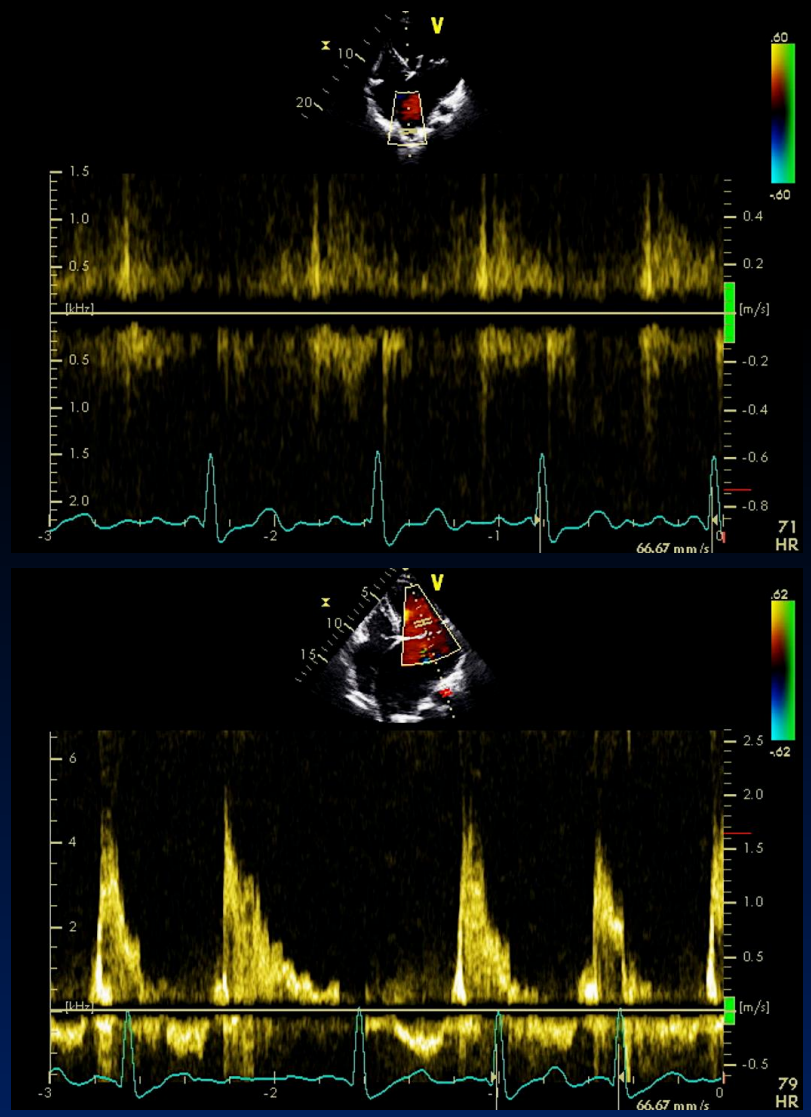


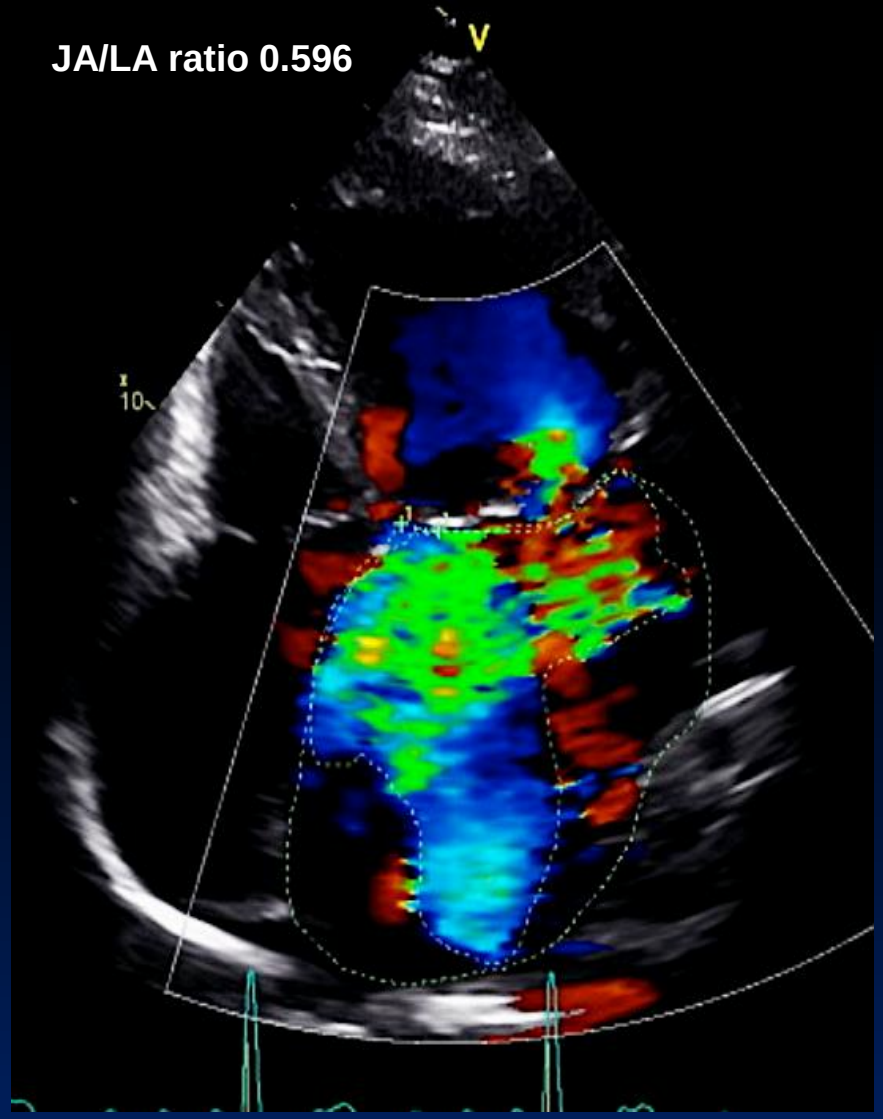


- Case (1) -



- Case (1) -

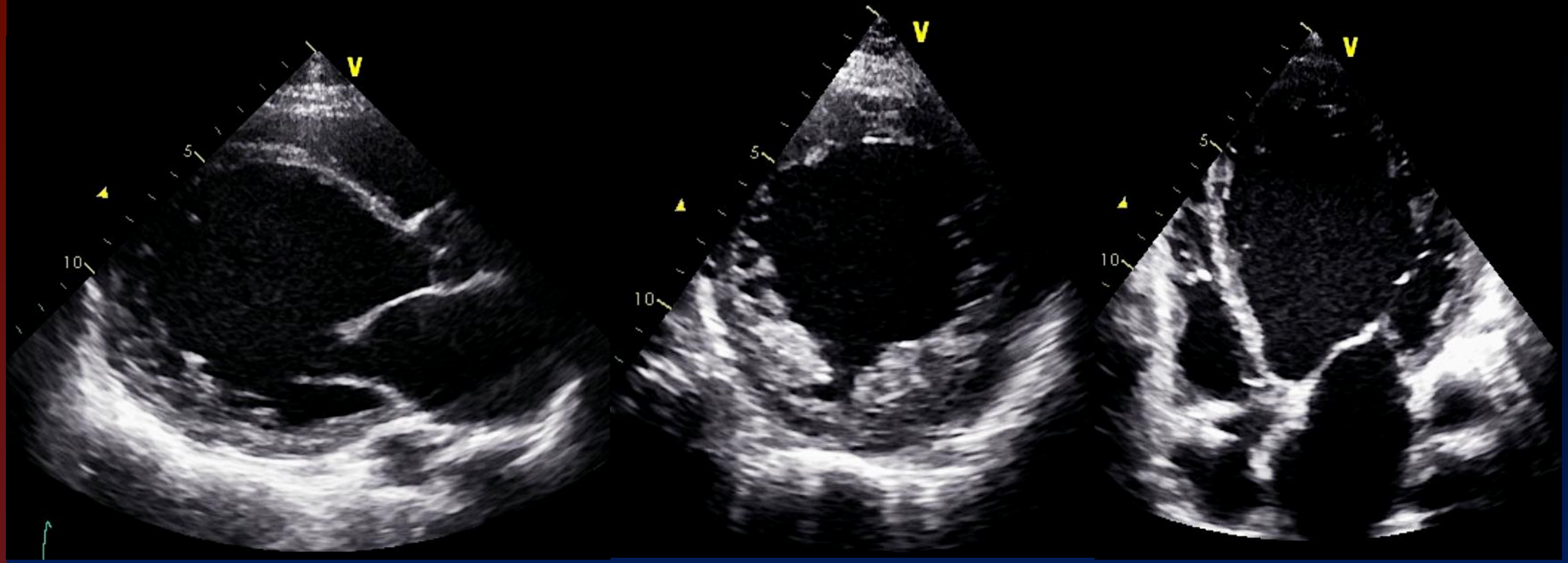




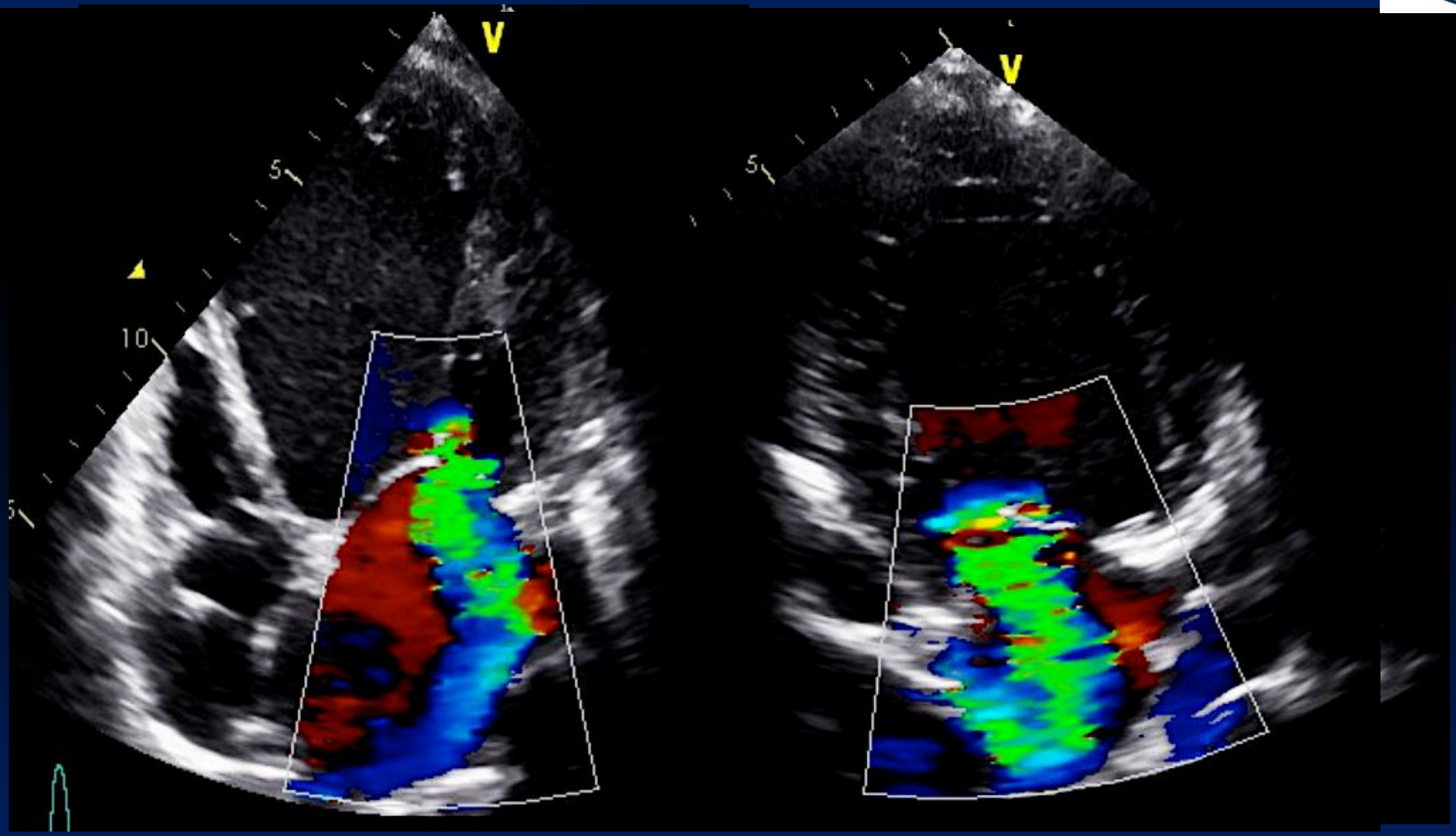
RF 63%
RV 84 mL
RoA 0.65 cm^2

- Case (2) -

55-year-old female with non-ischemic dilated cardiomyopathy with severe LV systolic dysfunction (LVEF ~20%), chronic kidney disease (eGFR= 35 ml/min), permanent AF, prior VF arrest post CRT-D implantation, recurrent hospitalizations for decompensated HF despite optimal GDMT, severe pulmonary hypertension (mean PA pressure 50 mmHg from right heart catheterization)

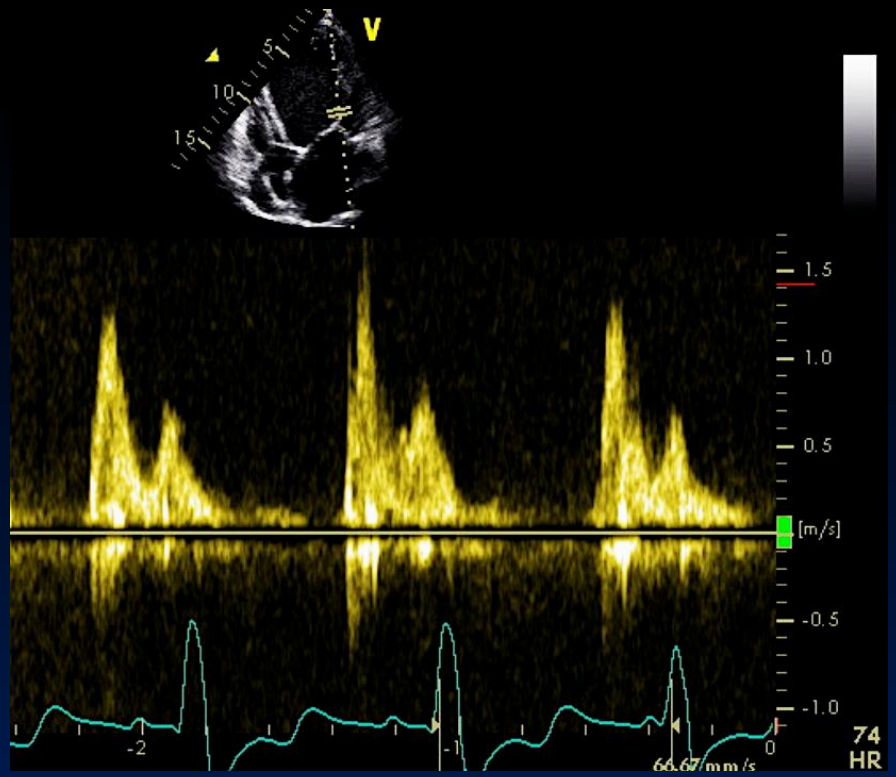


- Case (2) -

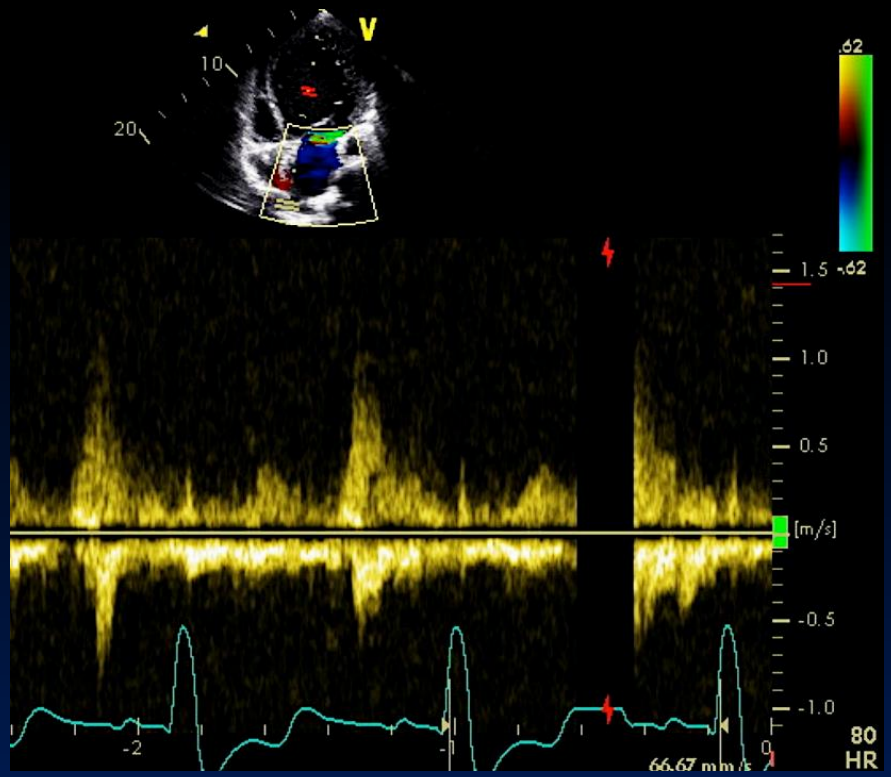


- Case (1) -

MV inflow velocity



PV doppler flow & velocities



RF 55%
RV 60 mL
RoA 0.43 cm^2

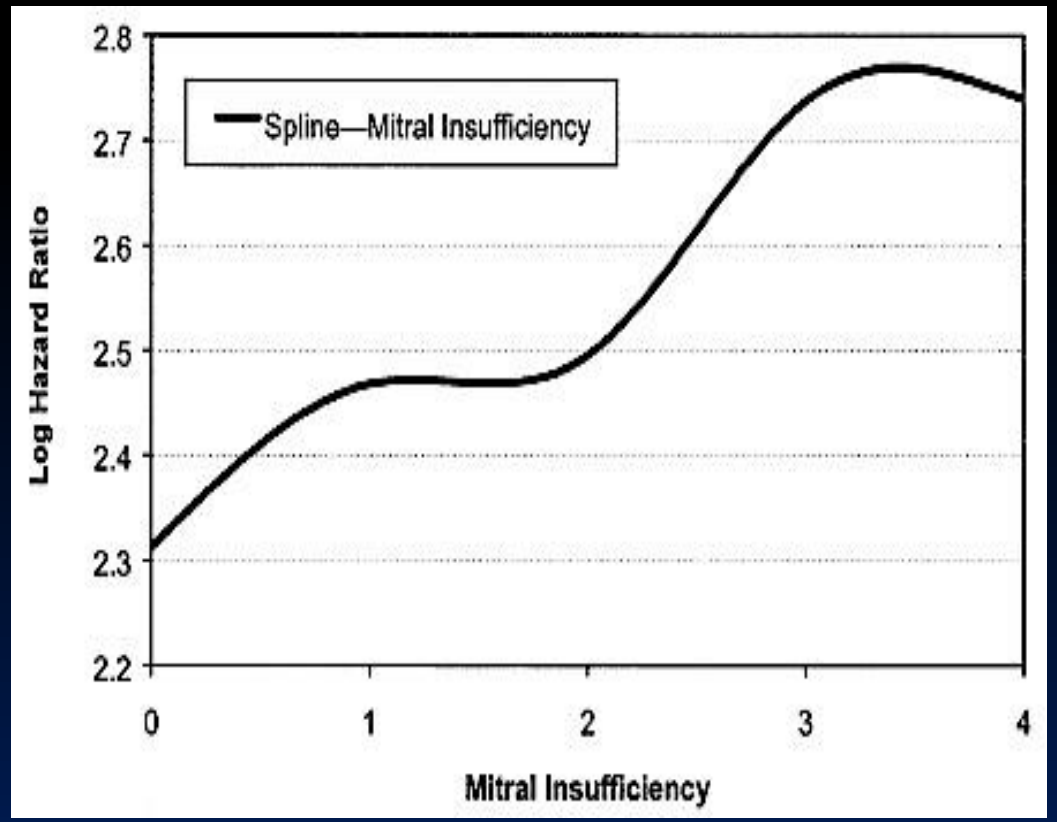
Indications for percutaneous edge-to-edge treatment in mitral regurgitation

Optimal valve morphology	Conditionally suitable valve morphology	Unsuitable valve morphology
Central pathology in segment 2	Pathology in segment 1 or 3	Perforated mitral valve leaflet of cleft
No leaflet calcification	Mild calcification outside the grip zone of the clip	Severe calcification in the grip zone
Mitral valve opening >4 cm^2	Mitral valve opening area >3 cm^2 with good residual mobility	Hemodynamically significant mitral stenosis (valve area <3 cm^2, mean gradient >5 mmHg)
Mobile length of the posterior leaflet ≥10 cm	Mobile lenth of the posterior leaflet 7-10 mm	Mobile length of the posterior leaflet <7 mm
Coaptation depth <11 mm	Coaptation depth ≥11 mm	
Normal leaflet strength and mobility	Leaflet restriction in systole (Carpentier IIIB)	Rheumatic leaflet thickening and restriction in systole and diastole (Carpentier IIIA)
Flail width <15 mm Flail gap <10 mm	Flail width >15 mm only with a large ring width and the option for multiple clips	Barlow's syndrome with multisegment flail leaflets.

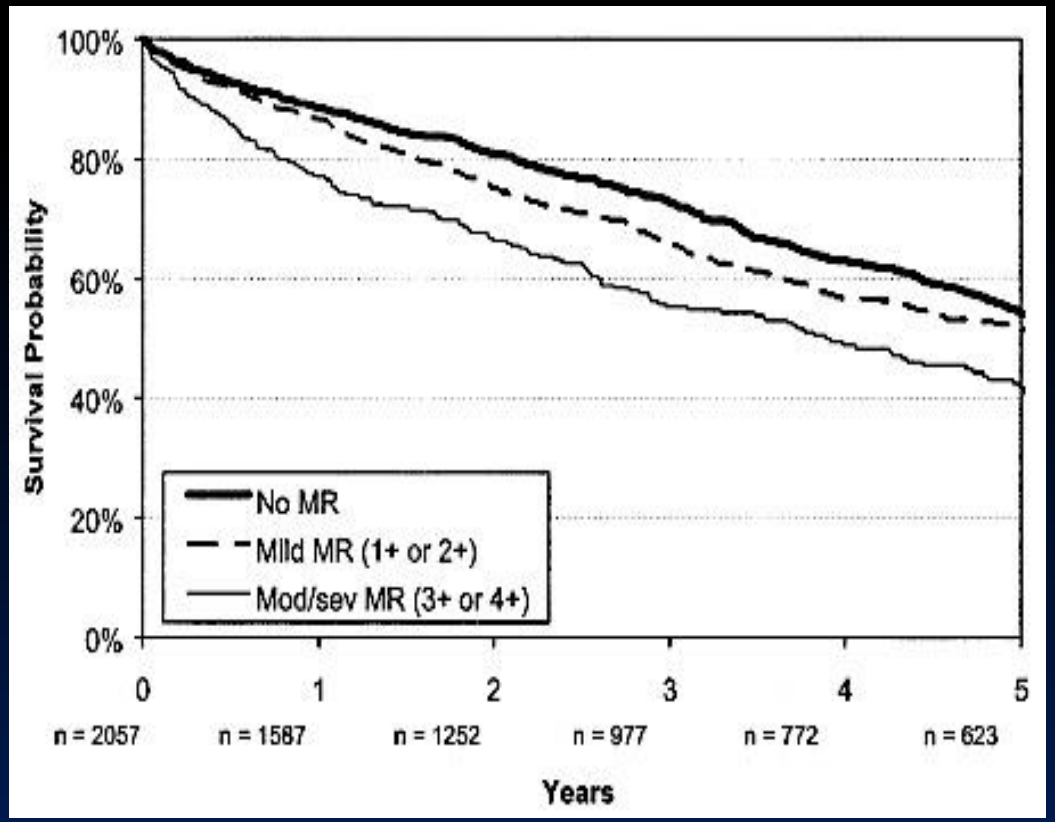
Boekstegers P, et al. Clin Res Control 2014; 103: 85-96

Does the presence of 'functional' MR portend worse outcomes?

Relation of frequency and severity of mitral regurgitation to survival among patients with left ventricular systolic dysfunction and heart failure



Relation between MR grade and hazard (risk) of death

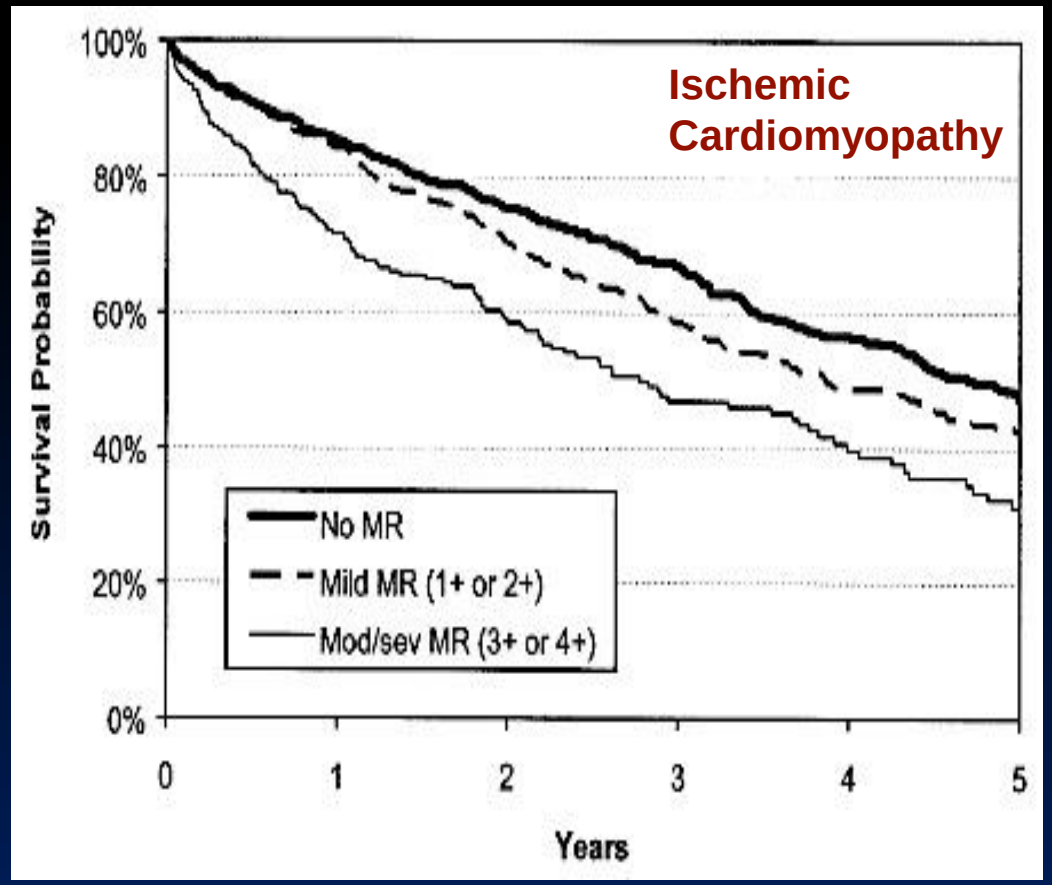


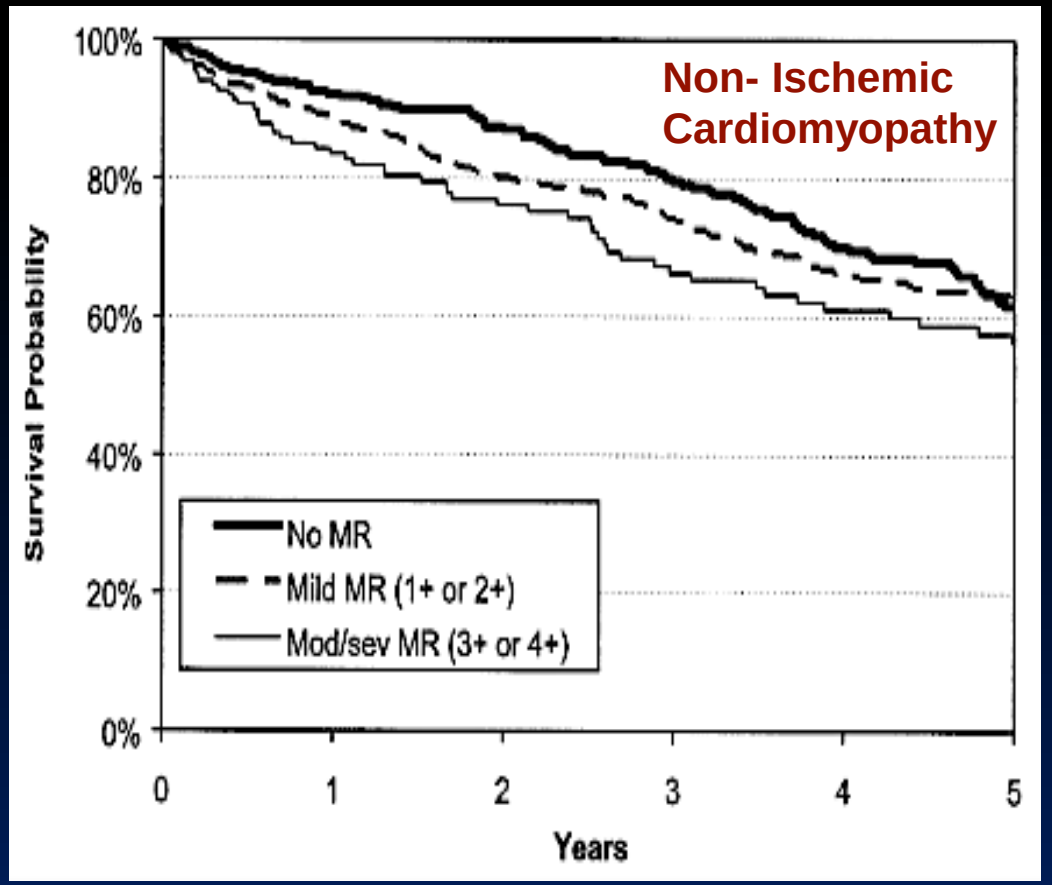
Adjusted survival estimates

Schofer J, et al. Circulation 2009; 120: 326-333

Does the presence of 'functional' MR portend worse outcomes?

Relation of frequency and severity of mitral regurgitation to survival among patients with left ventricular systolic dysfunction and heart failure

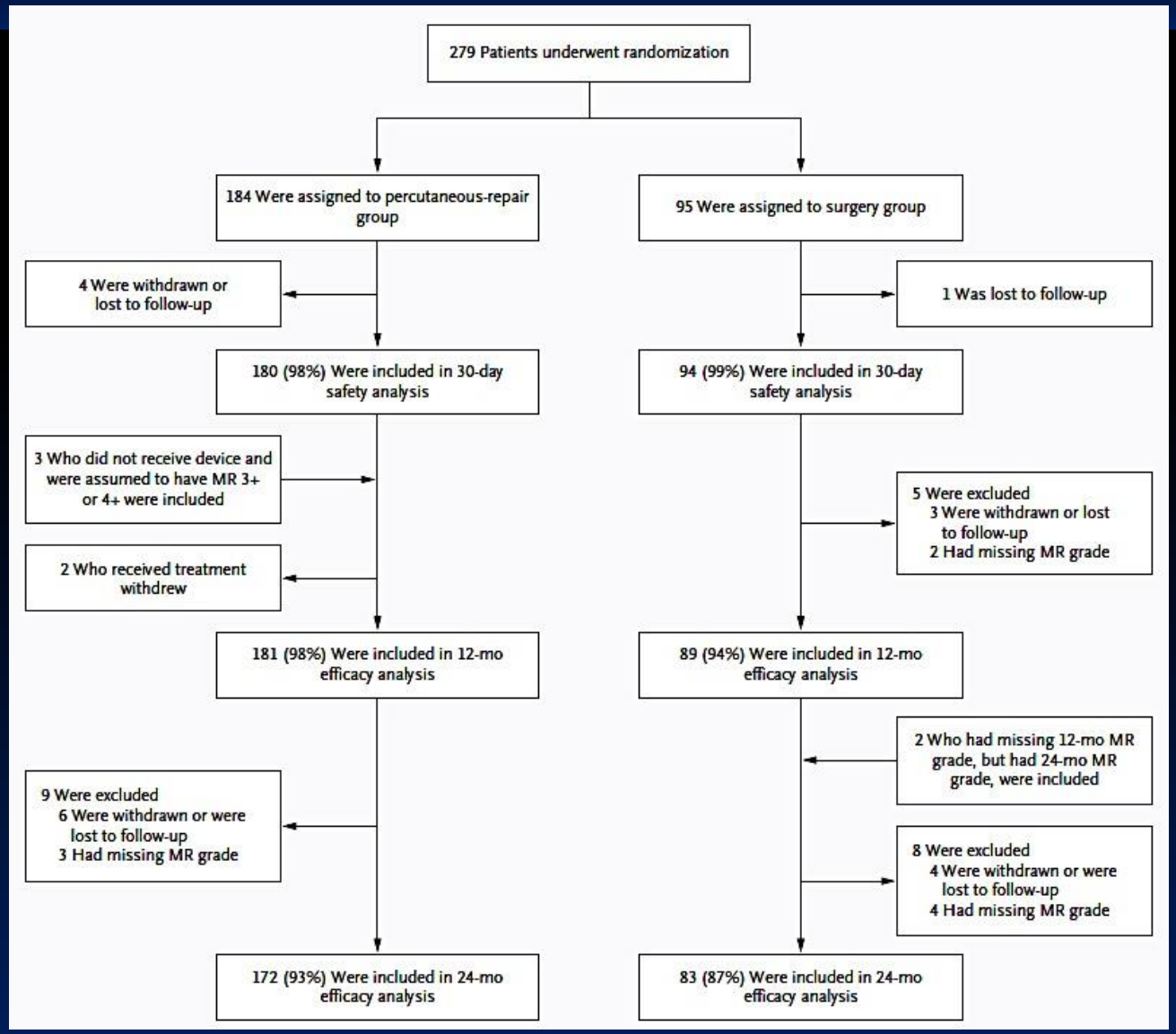




Schofer J, et al. Circulation 2009; 120: 326-333

Percutaneous Repair or Surgery for Mitral Regurgitation

- The EVEREST II Trial -



Feldman T, et al. N Engl J Med 2011; 364: 1395-1406

Percutaneous Repair or Surgery for Mitral Regurgitation

- The EVEREST II Trial -

Primary Efficacy End Point at 12 months in the intention-to-treat population

Event	Percutaneous Repair	Surgery	P Value
	no. (%)		
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. N Engl J Med 2011; 364: 1395-1406

Percutaneous Repair or Surgery for Mitral Regurgitation

- The EVEREST II Trial -

Major Adverse Events at 30 days in the intention-to-treat population

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
Death	2 (1)	2 (2)	0.89
Myocardial infarction	0	0	NA
Reoperation for failed surgical repair or replacement	0	1 (1)	0.74
Urgent or emergency cardiovascular surgery for adverse event	4 (2)	4 (4)	0.57
Major stroke	2 (1)‖	2 (2)	0.89
Renal failure	1 (<1)	0	1.00
Deep wound infection	0	0	NA
Mechanical ventilation for >48 hr	0	4 (4)	0.02
Gastrointestinal complication requiring surgery	2 (1)	0	0.78
New onset of permanent atrial fibrillation	2 (1)	0	0.78
Septicemia	0	0	NA
Transfusion of ≥2 units of blood	24 (13)	42 (45)	<0.001

Feldman T, et al. N Engl J Med 2011; 364: 1395-1406

Contemporary Management of Chronic Severe Mitral Regurgitation

.avi format media slides for presentation

Percutaneous Repair or Surgery for Mitral Regurgitation

- The EVEREST II Trial -

Primary Efficacy end point at 12 months of follow in the intention-to-treat population

Event	Percutaneous Repair No.(%)	Surgery No.(%)	P Value
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. N Engl J Med 2011; 364: 1395-1406

Percutaneous Repair or Surgery for Mitral Regurgitation

- The EVEREST II Trial -

Major adverse event at 30 days

Event	Percutaneous Repair No.(%)	Surgery No.(%)	P Value
Any major adverse event	27(15)	45(48)	<0.001
Any major adverse event excluding transfusion	9(5)	9(10)	0.23
Death	2(1)	2(2)	0.89
Myocardial infarction	0	0	NA
Re-operation for failed surgical repair or replacement	0	1(1)	0.74
Urgent or emergency cardiovascular surgery for adverse event	4(2)	4(4)	0.57
Major stroke	2(1)	2(2)	0.89
Renal failure	1(<1)	0	1.00
Deep wound infection	0	0	NA
Mechanical ventilation for >48 hours	0	4(4)	0.02
Gastrointestinal complications requiring surgery	2(1)	0	0.78
New onset permanent atrial fibrillation	2(1)	0	0.78
Septicemia	0	0	NA
Transfusion of >2 units of blood	24(13)	42(45)	<0.001

Feldman T, et al. N Engl J Med 2011; 364: 1395-1406

Transcatheter Mitral Valve Repair

- Leaflet Repair -

Alfieri Stitch **MitraClip®**