Management of Secondary MR : Insights from CTSN Ischemic MR trial; COAPT and MITRA-FR:

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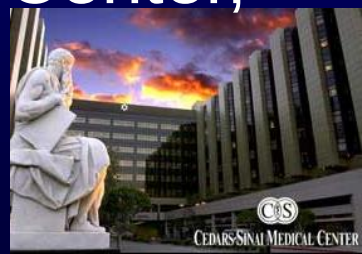

Disclosure Statement of Financial Interest
Saibal Kar

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

Affiliation/Financial Relationship	Company
• Grant/Research Support	• Abbott Vascular, Boston Scientific, Gore Medical, Edwards Lifesciences,
• Consulting Fees/Honoraria	• Abbott Vascular, Boston Scientific, Gore Medical,
• Other Financial Benefit	• Valcare

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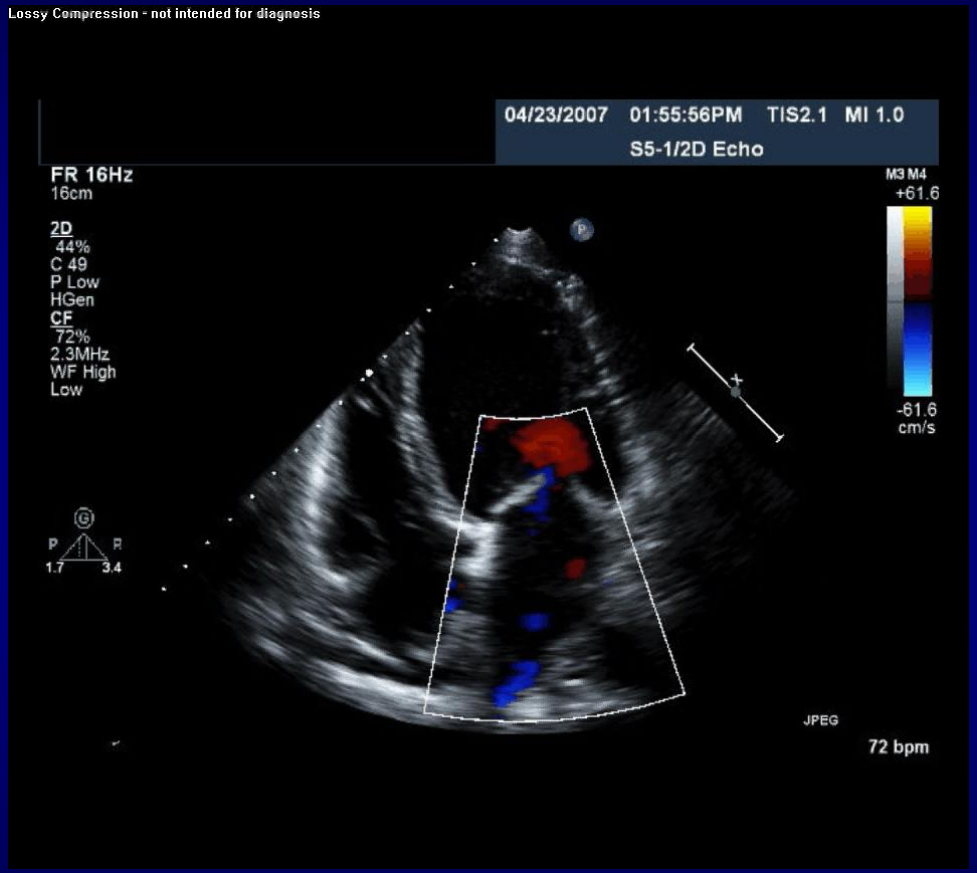
Functional(Secondary) Mitral Regurgitation (FMR)

An unmet clinical need

- Leaflets & chordae have no obvious structural abnormality
- Malcoaptation of leaflets due to Left ventricular Dysfunction
- More common than primary MR



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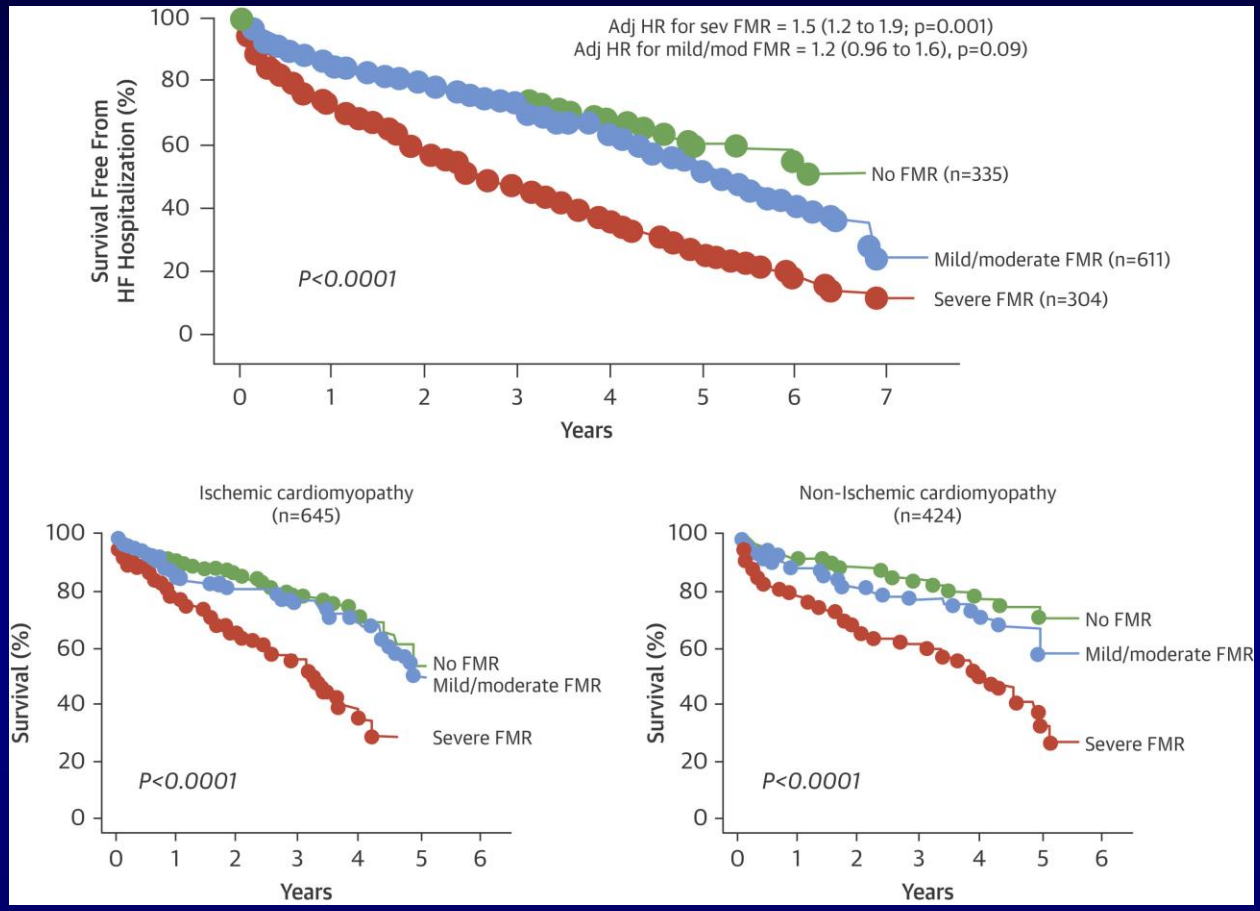
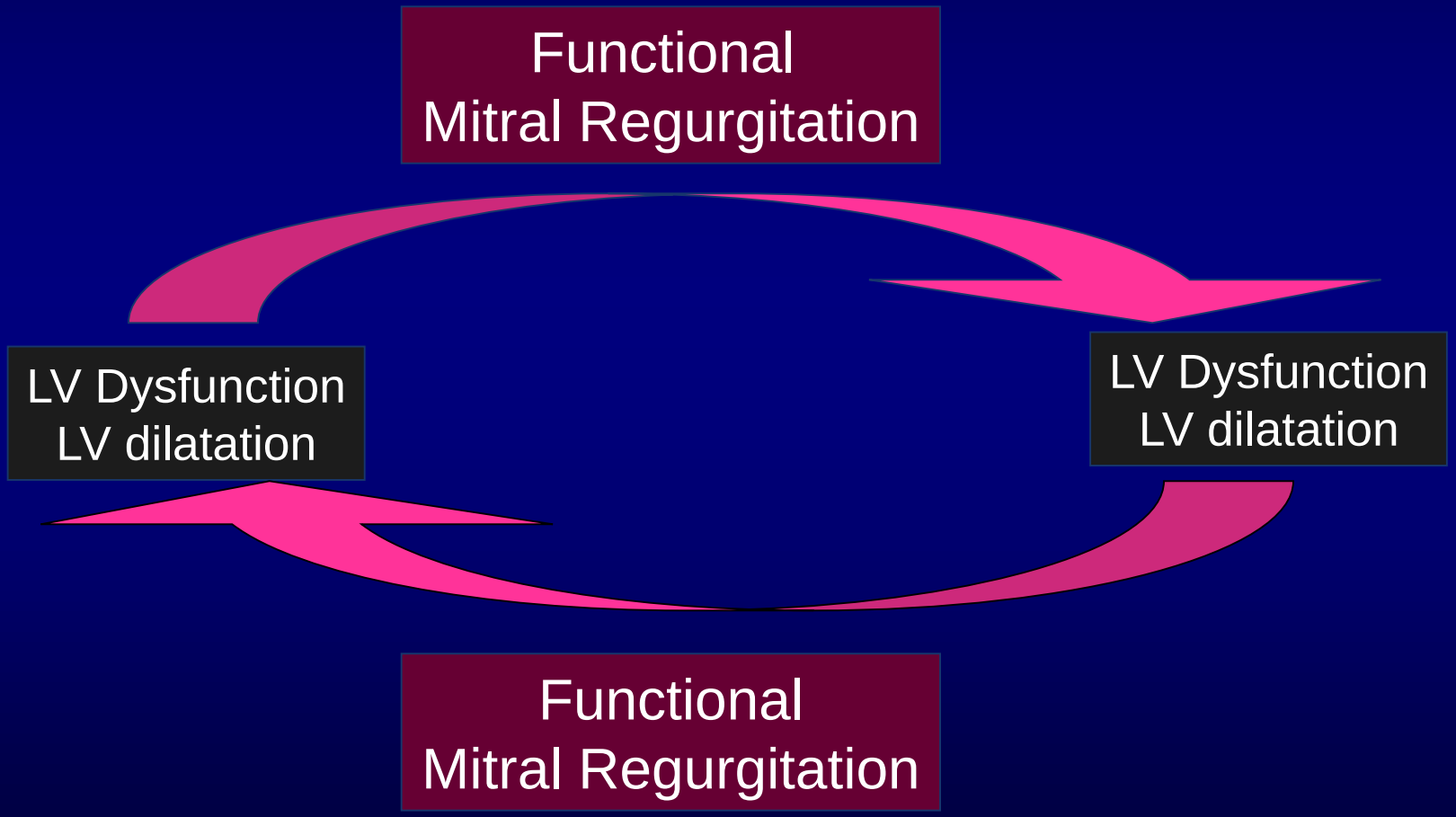
Prognosis of FMR based on severity of MR



(Top) Freedom from death or heart failure (HF) hospitalization in 1,256 patients according to the degree of functional mitral regurgitation (FMR). **(Bottom)** Freedom from death according to the degree of FMR in patients with ischemic **(lower left)** and nonischemic **(lower right)** cardiomyopathy

Rossi et al. Heart 2011: 1675-1680

FMR and LV dysfunction



Treatment of Secondary MR

- **Goals of therapy**
  - Improve symptoms
  - Reduce rate of re-hospitalizations for HF
  - Potentially improve survival

- **Treatment options**
  - Guideline directed medical therapy including Cardiac resynchronization therapy (CRTP) when appropriate
  - Surgery (repair or replacement)
  - Transcatheter mitral valve repair/replacement

Surgery for Secondary MR

- Mitral valve repair or replacement
- Mitral valve repair is usually Ring annuloplasty
- High recurrence rate following repair
- Symptomatic improvement
- No definite evidence of reduction of hospitalizations for HF
- No clear evidence of survival benefit
- New evidence of comparing Replacement versus Repair.

CTSN Ischemic MR Trial

ORIGINAL ARTICLE

Mitral-Valve Repair versus Replacement for Severe Ischemic Mitral Regurgitation

Michael A. Acker, M.D., Michael K. Parides, Ph.D., Louis P. Perrault, M.D., Alan J. Moskowitz, M.D., Annetine C. Gelijns, Ph.D., Pierre Voisine, M.D., Peter K. Smith, M.D., Judy W. Hung, M.D., Eugene H. Blackstone, M.D., John D. Puskas, M.D., Michael Argenziano, M.D., James S. Gammie, M.D., Michael Mack, M.D., Deborah D. Ascheim, M.D., Emilia Bagiella, Ph.D., Ellen G. Moquete, R.N., T. Bruce Ferguson, M.D., Keith A. Horvath, M.D., Nancy L. Geller, Ph.D., Marissa A. Miller, D.V.M., Y. Joseph Woo, M.D., David A. D'Alessandro, M.D., Gorav Ailawadi, M.D., Francois Dagenais, M.D., Timothy J. Gardner, M.D., Patrick T. O'Gara, M.D., Robert E. Michler, M.D., and Irving L. Kron, M.D., for the CTSN*

/ ENGLAND JOURNAL of MEDICINE

Acker et al. N Engl J Med. 2014 Jan 2;370(1):23-32

ORIGINAL ARTICLE

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

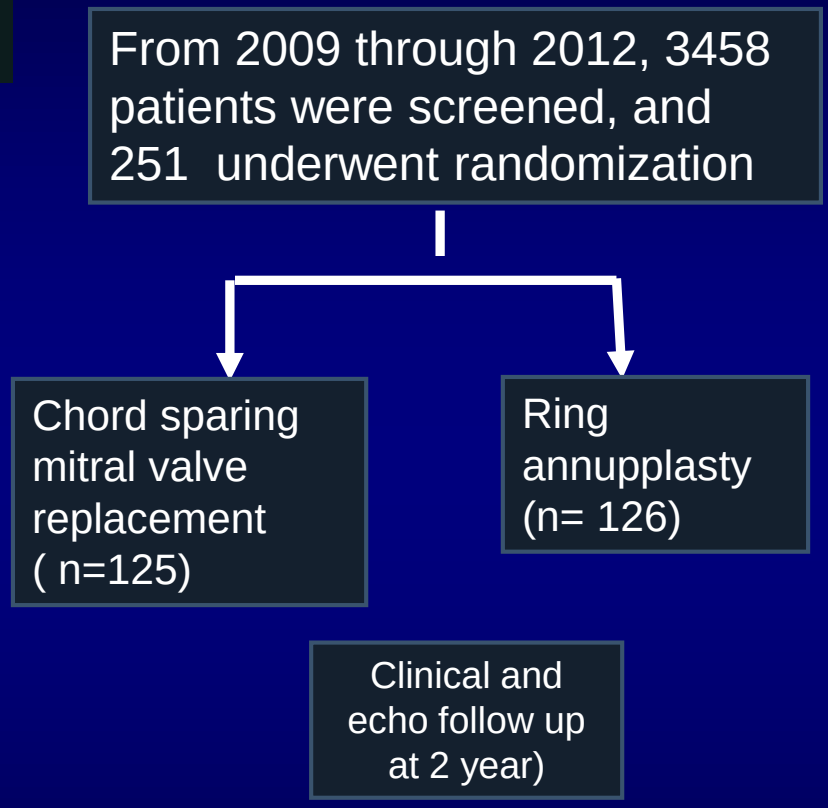
D. Goldstein, A.J. Moskowitz, A.C. Gelijns, G. Ailawadi, M.K. Parides, L.P. Perrault, J.W. Hung, P. Voisine, F. Dagenais, A.M. Gillinov, V. Thourani, M. Argenziano, J.S. Gammie, M. Mack, P. Demers, P. Atluri, E.A. Rose, K. O'Sullivan, D.L. Williams, E. Bagiella, R.E. Michler, R.D. Weisel, M.A. Miller, N.L. Geller, W.C. Taddei-Peters, P.K. Smith, E. Moquete, J.R. Overbey, I.L. Kron, P.T. O'Gara, and M.A. Acker, for the CTSN*

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

Replacement vs Repair for Secondary MR (CTSN)

Design

- DESIGN: Prospective, randomized, multicenter study
- PRIMARY END POINT: left ventricular reverse remodeling, as assessed by means of the left ventricular end-systolic volume index (LVESVI) on the basis of transthoracic echocardiography performed 12 months after randomization
- SECONDARY ENDPOINT:
- Mortality, MACE, recurrence of MR, readmissions of HF, quality of life



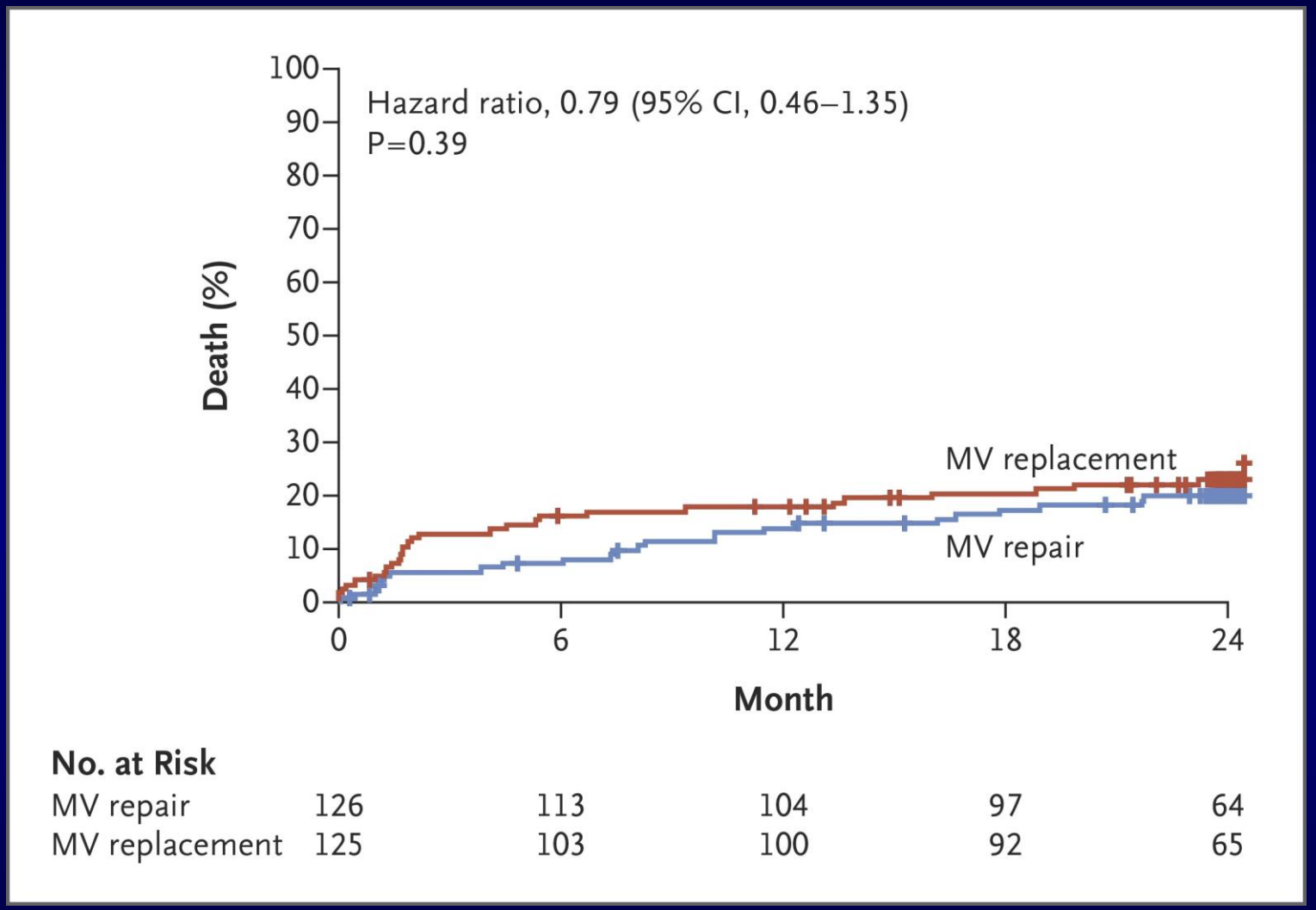
Results of CTSN Trial

- No significant difference in left ventricular reverse remodeling at 12 months and 2 years between the two groups

- In surviving patients there was higher degree recurrence of moderate or severe mitral regurgitation(MR) in repair versus replacement (32.6% [28.4% moderate and 4.2% severe] vs. 2.3% [all moderate]; P<0.001) at 12 months

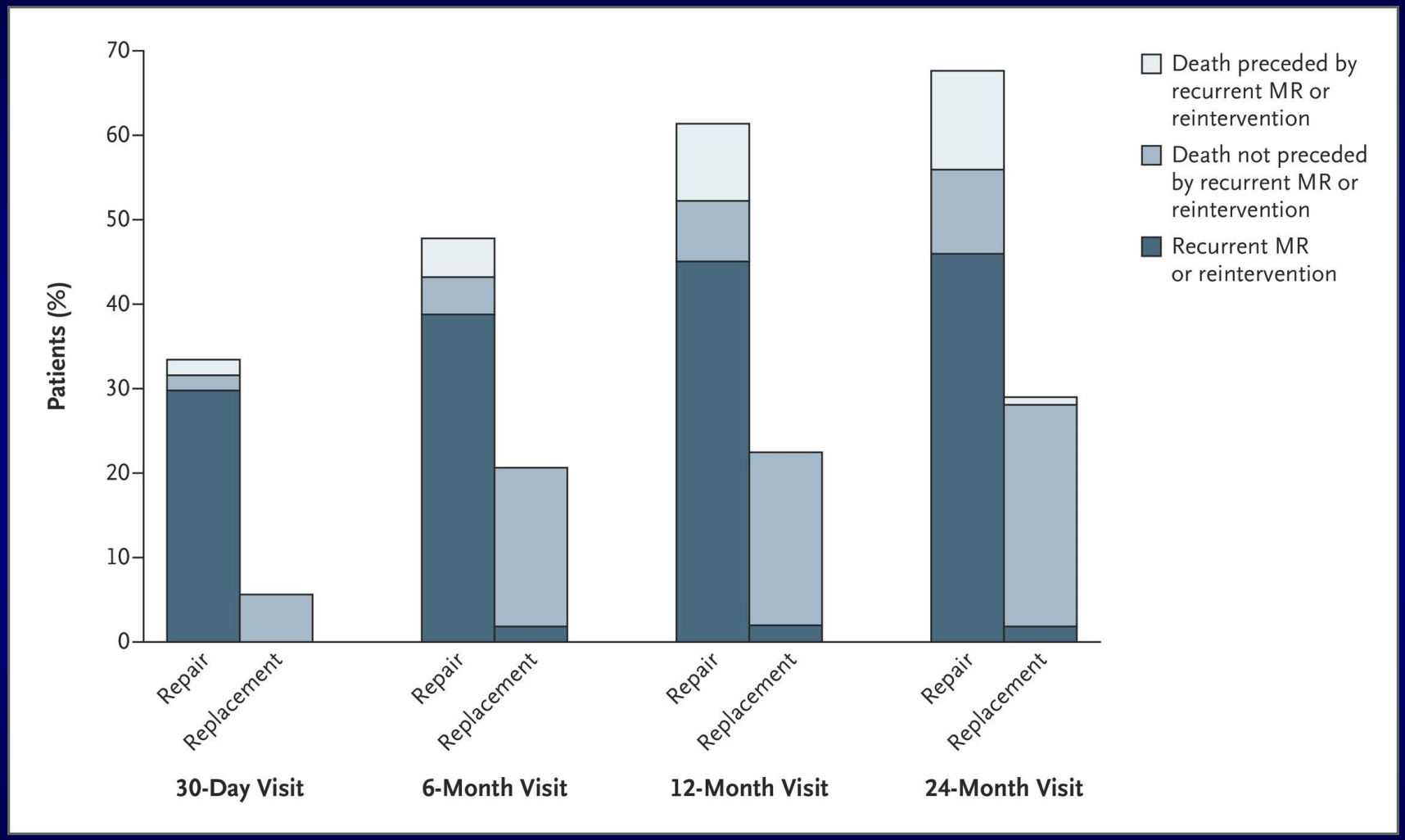
- In the repair group, the 12-month LVESVI was 64.1±23.9 ml/m2 in pts with recurrent MR versus 47.3±23.0 ml/m2 in those without recurrent MR (P<0.001).

Time-to-Event Curves for Death.



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

Cumulative Failure of Mitral-Valve Repair or Replacement.



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

Conclusions

- Among patients with severe ischemic mitral regurgitation who were assigned to mitral-valve repair or replacement, there were no significant between-group differences in left ventricular remodeling or mortality at 2 years.

- Mitral regurgitation recurred more frequently in the repair group which resulted in more heart failure related adverse events and cardiac admissions

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

Transcatheter mitral valve repair for secondary MR

- > 70,000 pts have been treated with MitraClip
  - Majority of patients are secondary MR
- It is safe, and effective and there is suggestion of improvement of symptoms and reduction of hosptilization
- New data is available of MitraClip versus medical therapy

MitraClip for FMR
Rationale

- Helps in coaptation of leaflets
- Restricts annular dilatation
- Helps in maintaining of LV geometry “rein effect

FMR and LV dysfunction

Functional
Mitral Regurgitation

LV Dysfunction
LV dilatation

LV Dysfunction
LV dilatation

Functional
Mitral Regurgitation

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Mitra-Fr Trial

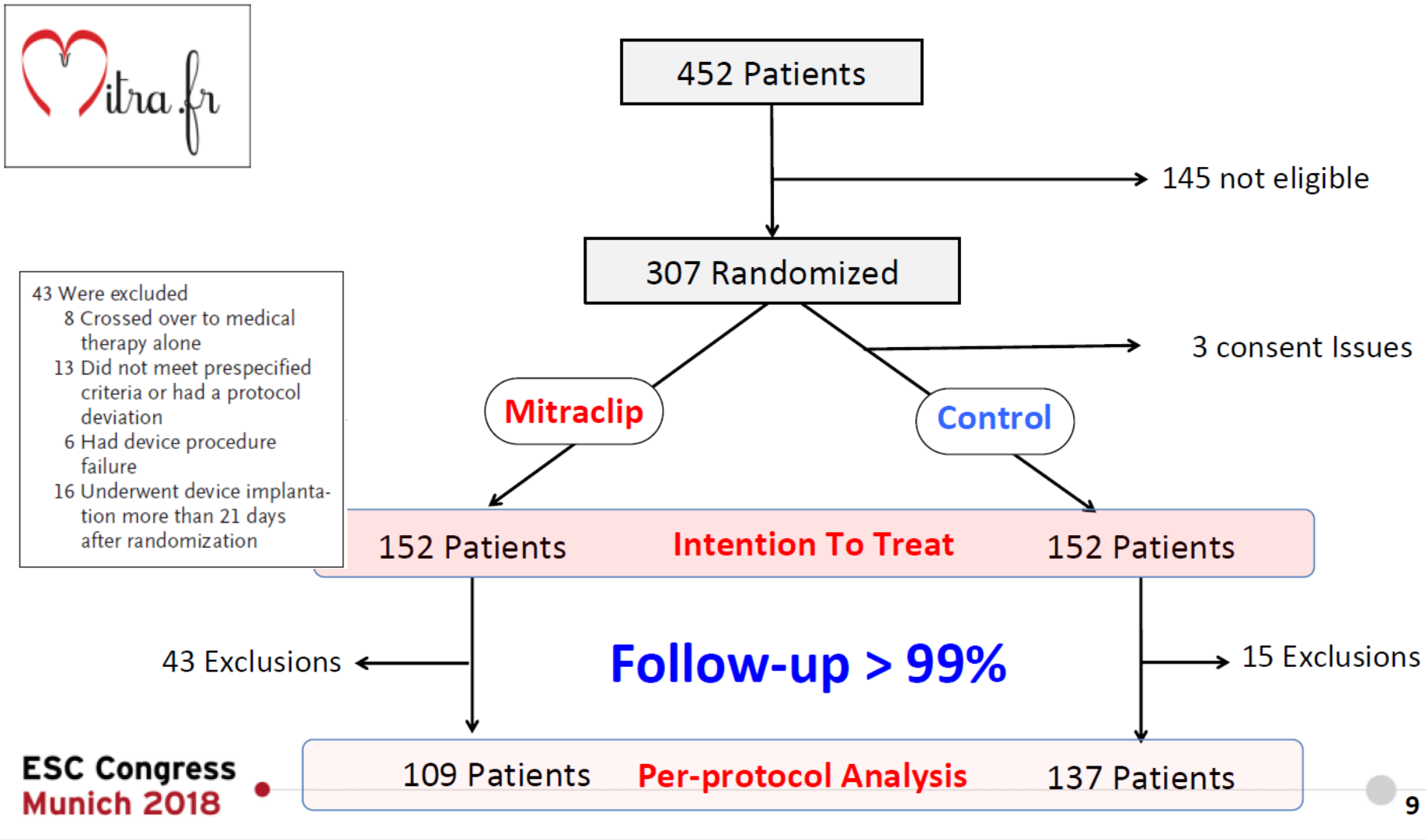
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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*

N Engl J Med. 2018 Aug 27. doi: 10.1056



Mitra Fr : Study Design

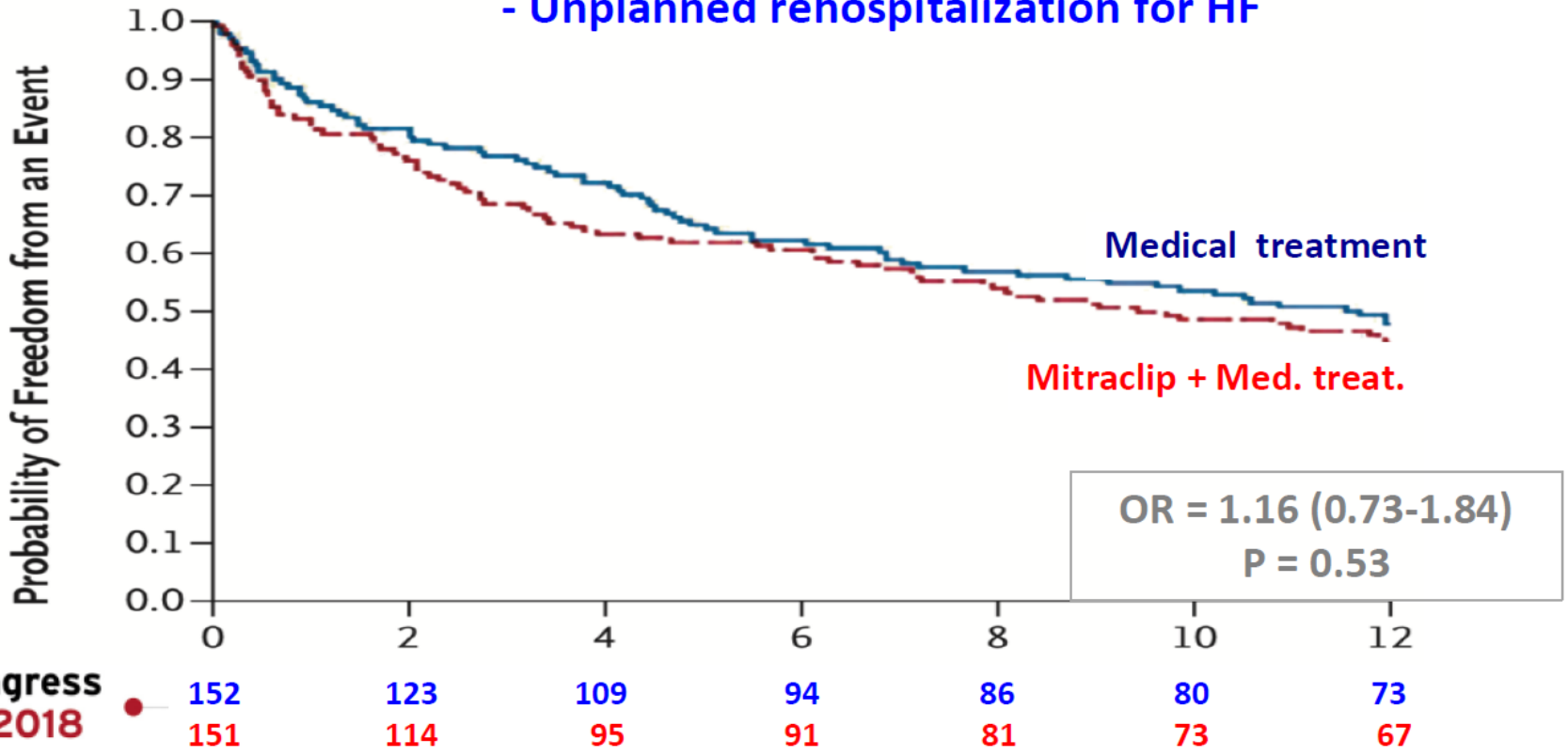
- **Objective**: Evaluation of MitraClip + Medical therapy vs medical therapy alone in patients with HF and severe secondary MR

- **Primary Endpoint** "Composite" All cause death or unplanned rehospitalization for HF in 12 months

- **Important inclusion criteria**
  - Symptomatic despite optimal medical Rx (NYHA ≥ 2)
  - EF: 15 – 40%, NYHA
  - Severe secondary MR (ESC criteria) ERO > 0.2 sq cm
  - No eligible for surgery based on local heart team approach

Primary composite endpoint *(99% follow-up)*

- All-Cause Death
- Unplanned rehospitalization for HF



ESC Congress
Munich 2018

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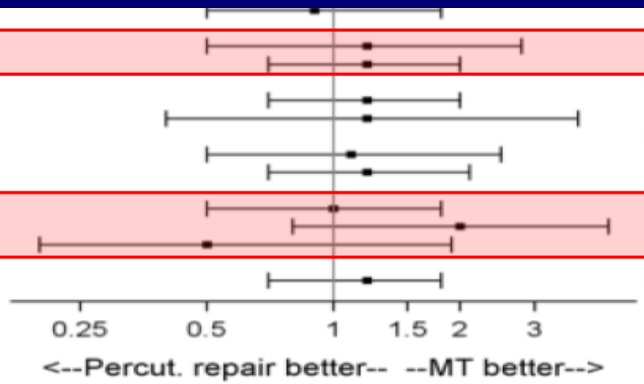
≥ Median	38/72	(52.8)	42/80	(52.5)	0.90 (0.50, 1.80)	
LVEF						0.99
< 30%	21/35	(60.0)	27/48	(56.3)	1.20 (0.50, 2.80)	
≥ 30%	62/115	(53.9)	51/102	(50.0)	1.20 (0.70, 2.00)	
TRICUSPID REGURGITATION						0.93
Mild	60/110	(54.5)	60/118	(50.8)	1.20 (0.70, 2.00)	
Moderate/Severe	19/29	(65.5)	14/23	(60.9)	1.20 (0.40, 3.80)	
LV TELEDIASTOLIC DIAMETER						0.84
< 65 mm	21/43	(48.8)	21/45	(46.7)	1.10 (0.50, 2.50)	
≥ 65 mm	62/107	(57.9)	56/105	(53.3)	1.20 (0.70, 2.10)	
MITRAL REGURGITANT ORIFICE						0.85
< 30 mm2	37/77	(48.1)	39/80	(48.8)	1.00 (0.50, 1.80)	
30-40 mm2	28/44	(63.6)	24/51	(47.1)	2.00 (0.80, 4.50)	
> 40 mm2	18/29	(62.1)	15/20	(75.0)	0.50 (0.20, 1.90)	
OVERALL	83/150	(55.3)	78/151	(51.7)	1.20 (0.70, 1.80)	0.53



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Mitra-Fr Summary

- At one year there was no difference of the composite end point of death and HF rehospitalization between groups
- Limitations
  - Small sample size, too short follow up
  - In 9%, procedure was not performed
  - Less severe degree of MR

Limitations of Mitra Fr trial

- Small numbers: Difficult to make any subgroup analysis
- Multiple exclusions 43 out of 150 pts excluded after randomization
- Included pts with less severe degree of MR (ERO > 20 ml were included) and large ventricles
- No central eligibility committee
- High initial failure and complication rate
- Missing data on quality of life, echos
- In-experienced operators (only 5 cases before they randomized patients
- Higher late recurrence of MR
- Only one year follow up

Then on Sept 28th 2018

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

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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*

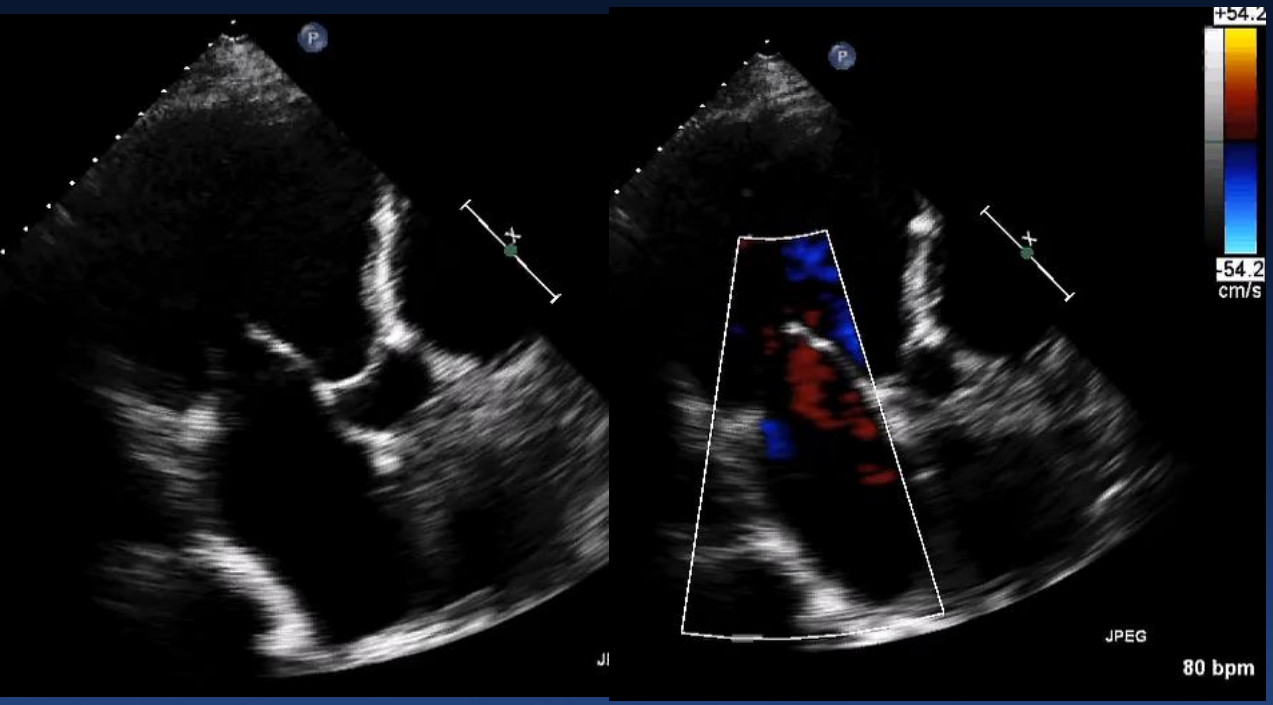
COAPT TRIAL

Key Inclusion Criteria

1. Ischemic or non-ischemic cardiomyopathy with LVEF 20%-50% and LVESD ≤70 mm
2. Moderate-to-severe (3+) or severe (4+) secondary MR confirmed by an independent echo core laboratory prior to enrollment (US ASE criteria)
3. NYHA functional class II-IVa (ambulatory) despite a stable maximally-tolerated GDMT regimen and CRT (if appropriate) per societal guidelines
4. 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*
5. Not appropriate for mitral valve surgery by local heart team assessment
6. IC believes secondary MR can be successfully treated by the MitraClip

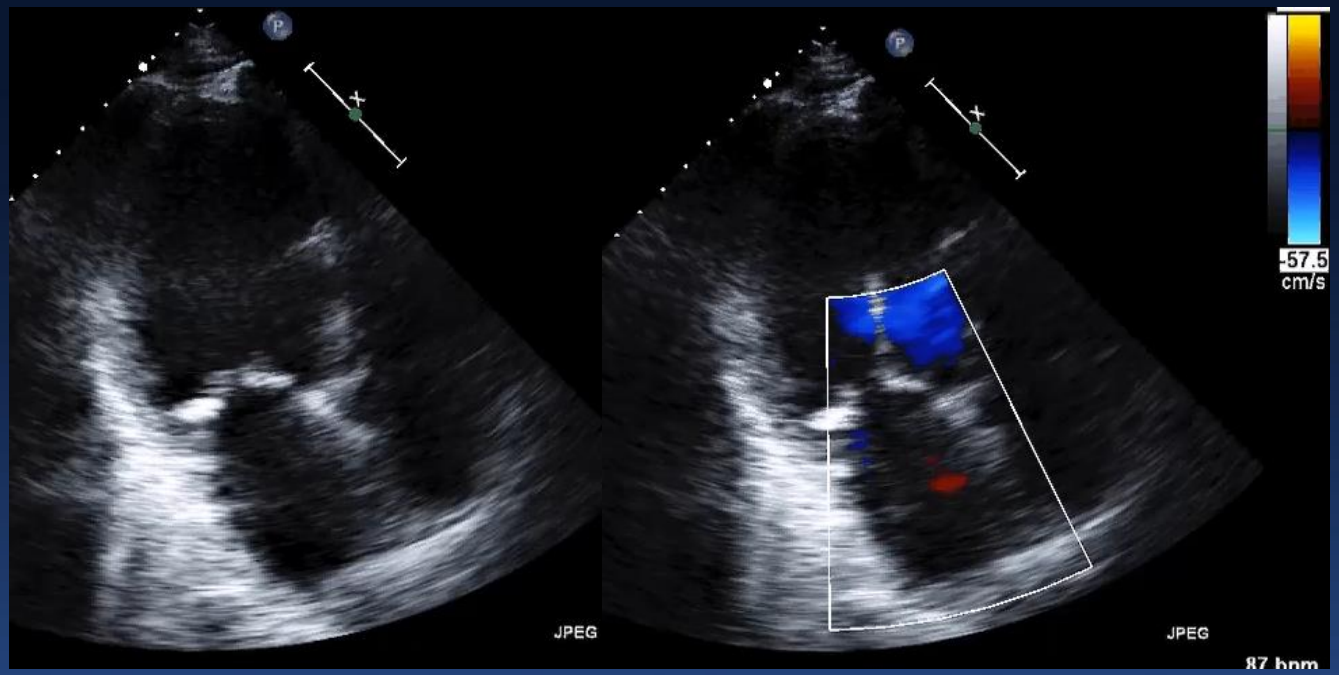
Adjusted by a 4% reduction in the BNP or NT-proBNP cutoff for every increase of 1 kg/m^2 in BMI >20 kg/m^2

Case 1: 58 yr old male with history of ischemic Cardiomyopathy, NYHA Class III, on max tolerated GDMT and CRTP



- LVEF = 20%
- ERO = 0.43 cm^2
- Reg Fraction 46%
- LVEDD 73 mm
- LVEDS 57 mm
- PA systolic 55 mm Hg

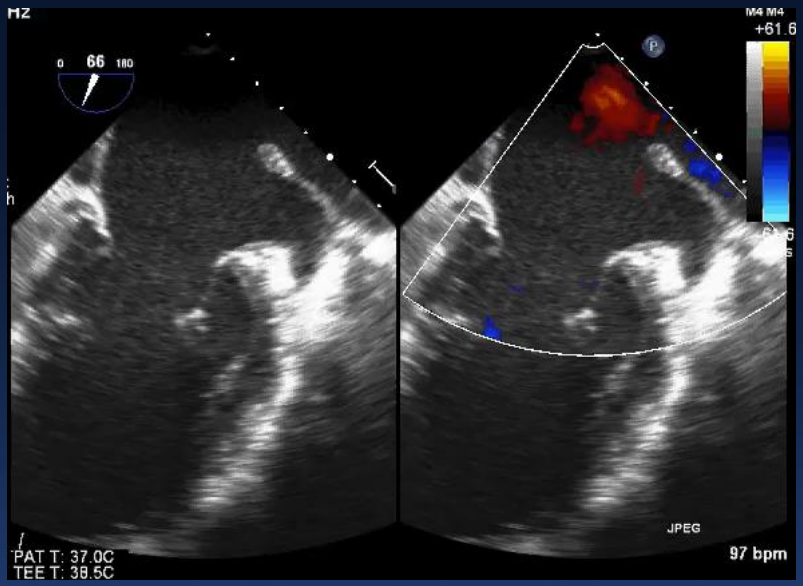
Case 2: 65 yr old male with ischemic cardiomyopathy on GDMT, narrow QRS, NYHA Class III



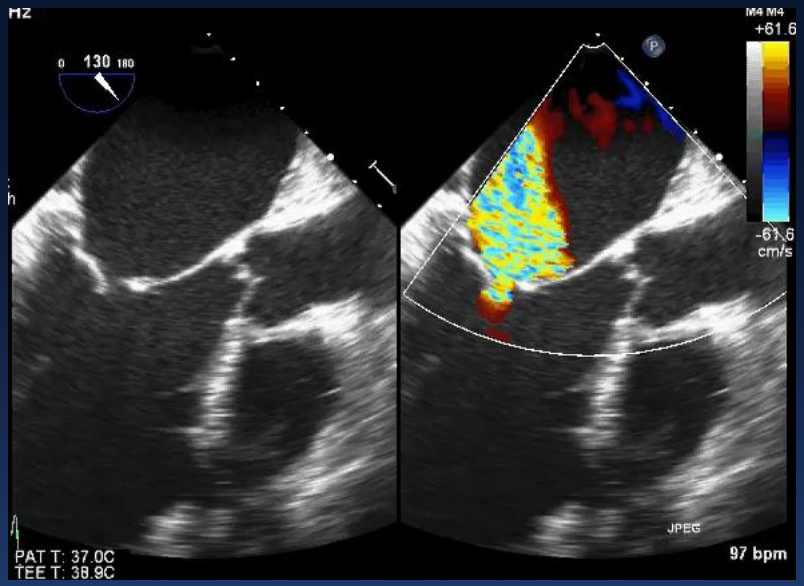
- LVEF = 25%
- ERO = 0.41 cm^2
- Reg Fraction 40%
- LVEDD 65 mm
- LVEDS 58 mm
- PA systolic 42 mm Hg

Baseline TEE : Dec 2014

Bicommissural view



LVOT view



COAPT TRIAL

Primary Endpoints

Primary effectiveness endpoint: All HF hospitalizations through 24 months*

Powered for superiority of the Device group compared with the Control group

Primary safety endpoint: Freedom at 12 mos from device-related complications:

- Single leaflet device attachment
- Device embolization
- Endocarditis requiring surgery
- Echo core laboratory-confirmed mitral stenosis requiring surgery
- Left ventricular assist device implant
- Heart transplant
- Any device-related complication requiring non-elective cardiovascular surgery

Powered for superiority of the Device group vs. a pre-specified OPG**

*Analyzed when the last subject completes 12 months of follow-up; **Objective performance goal

Powered Secondary Endpoints

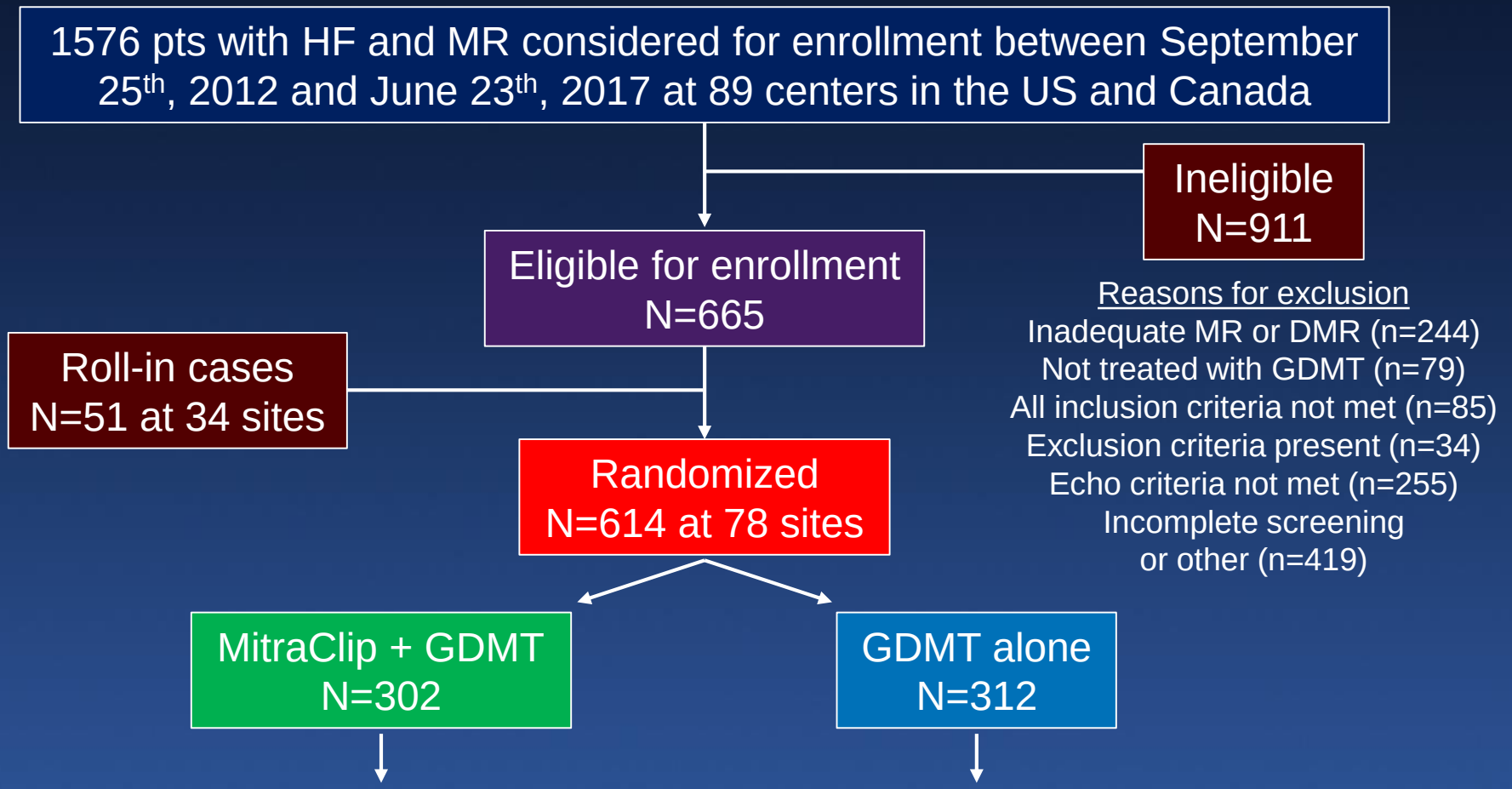
- Tested in hierarchical order[1] -

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 and win ratio analysis)
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]

[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

COAPT TRIAL

Study Flow and Follow-up



COAPT TRIAL

Top 10 Enrolling Sites

1. Saibal Kar	Cedars-Sinai Medical Center, Los Angeles, CA	n=46
2. Scott Lim	University of Virginia, Charlottesville, VA	n=30
3. Jacob Mishell	Kaiser Permanente, San Francisco, CA	n=29
4. Brian Whisenant	Intermountain Medical Center, Murray, UT	n=26
5. Paul Grayburn	Baylor Heart and Vascular Hospital, Dallas, TX	n=25
6. Andreas Brieke	University Of Colorado Hospital, Aurora, CO	n=17
6. Michael Rinaldi	Carolinas Medical Center, Charlotte, NC	n=17
6. Samir Kapadia	Cleveland Clinic, Cleveland, OH	n=17
6. Ian Sarembock	The Christ Hospital, Cincinnati, OH	n=17
6. Vivek Rajagopal	Piedmont Hospital, Atlanta, GA	n=17

COAPT TRIAL

Baseline Characteristics (i)

	MitraClip + GDMT (N=302)	GDMT alone (N=312)
Age (years)	71.7 ± 11.8	72.8 ± 10.5
Male	66.6%	61.5%
Diabetes	35.1%	39.4%
Hypertension	80.5%	80.4%
Hyperchol.	55.0%	52.2%
Prior MI	51.7%	51.3%
Prior PCI	43.0%	49.0%
Prior CABG	40.1%	40.4%
Prior stroke or TIA	18.5%	15.7%
PVD	17.2%	18.3%
COPD	23.5%	23.1%
H/o atrial fibr	57.3%	53.2%

	MitraClip + GDMT (N=302)	GDMT alone (N=312)
BMI (kg/m^2)	27.0 ± 5.8	27.1 ± 5.9
CrCl (ml/min)	50.9 ± 28.5	47.8 ± 25.0
- ≤60 ml/min	71.6%	75.2%
Anemia (WHO)	59.8%	62.7%
BNP (pg/mL)	1015 ± 1086	1017 ± 1219
NT-proBNP (pg/mL)	5174 ± 6567	5944 ± 8438
STS replacement sc	7.8 ± 5.5	8.5 ± 6.2
- ≥8	41.7%	43.6%
Surgical risk (central eligibility committee)		
- High*	68.6%	69.9%
- Not-high	31.4%	30.1%

* STS repl score ≥8% or one or more factors present predicting extremely high surgical risk

Baseline Characteristics (ii)

HF parameters	MitraClip + GDMT (N=302)	GDMT alone (N=312)	Echo core lab	MitraClip + GDMT (N=302)	GDMT alone (N=312)
Etiology of HF			MR severity		
- Ischemic	60.9%	60.6%	- Mod-to-sev (3+)	49.0%	55.3%
- Non-ischemic	39.1%	39.4%	- Severe (4+)	51.0%	44.7%
NYHA class			EROA, cm^2	0.41 ± 0.15	0.40 ± 0.15
- I	0.3%	0%	LVESD, cm	5.3 ± 0.9	5.3 ± 0.9
- II	42.7%	35.4%	LVEDD, cm	6.2 ± 0.7	6.2 ± 0.8
- III	51.0%	54.0%	LVESV, mL	135.5 ± 56.1	134.3 ± 60.3
- IV	6.0%	10.6%	LVEDV, mL	194.4 ± 69.2	191.0 ± 72.9
HF hosp w/i 1 year	58.3%	56.1%	LVEF, %	31.3 ± 9.1	31.3 ± 9.6
Prior CRT	38.1%	34.9%	- ≤40%	82.2%	82.0%
Prior defibrillator	30.1%	32.4%	RVSP, mmHg	44.0 ± 13.4	44.6 ± 14.0

COAPT TRIAL

Medication Use at Baseline

Maximally-tolerated doses	MitraClip + GDMT (n=302)	GDMT alone (n=312)
Beta-blocker	91.1%	89.7%
ACEI, ARB or ARNI	71.5%	62.8%
Mineralocorticoid receptor antagonist	50.7%	49.7%
Nitrates	6.3%	8.0%
Hydralazine	16.6%	17.6%
Diuretic	89.4%	88.8%
Chronic oral anticoagulant	46.4%	40.1%
Aspirin	57.6%	64.7%
P2Y12 receptor inhibitor	25.2%	22.8%
Statin	62.6%	60.6%

COAPT TRIAL

Major Changes in HF Meds w/i 12 Months

	MitraClip + GDMT (n=302)	GDMT alone (n=312)	P value
ACEI, ARB or ARNI			
- ⇓ dose by >50% or discontinue	6.6%	4.8%	0.33
- ⇑ dose by >100% or new drug started	7.6%	7.4%	0.91
Beta-blocker			
- ⇓ dose by >50% or discontinue	5.3%	5.1%	0.92
- ⇑ dose by >100% or new drug started	8.6%	3.8%	0.01
Mineralocorticoid receptor antagonist			
- ⇓ dose by >50% or discontinue	0.7%	0.6%	1.00
- ⇑ dose by >100% or new drug started	5.3%	2.6%	0.08
Nitrates			
- ⇓ dose by >50% or discontinue	0.0%	0.0%	1.00
- ⇑ dose by >100% or new drug started	1.0%	1.9%	0.51
Hydralazine			
- ⇓ dose by >50% or discontinue	1.0%	0.0%	0.12
- ⇑ dose by >100% or new drug started	4.3%	3.8%	0.77

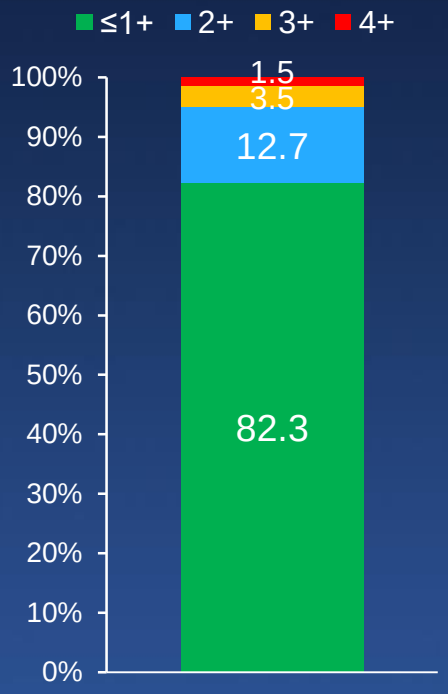
COAPT TRIAL

MitraClip Procedure (n=302)

MitraClip procedure attempted	293/302 (97.0%)
Clip implanted (MitraClip procedure attempted)	287/293 (98.0%)
Clip implanted (all patients)	287/302 (95.0%)
Mean # of clips implanted	1.7 ± 0.7 (n=293)
- 0 clips implanted	6 (2.0%)
- 1 clip implanted	106 (36.2%)
- 2 clips implanted	157 (53.6%)
- 3 clips implanted	23 (7.9%)
- 4 clips implanted	1 (0.3%)
Procedure duration (mins)	162.9 ± 118.1
- Device procedure time (mins)	118.9 ± 63.5
- Device time (mins)	82.7 ± 80.8
- Fluoroscopy time (mins)	33.9 ± 23.2

TTE at discharge (n=260)

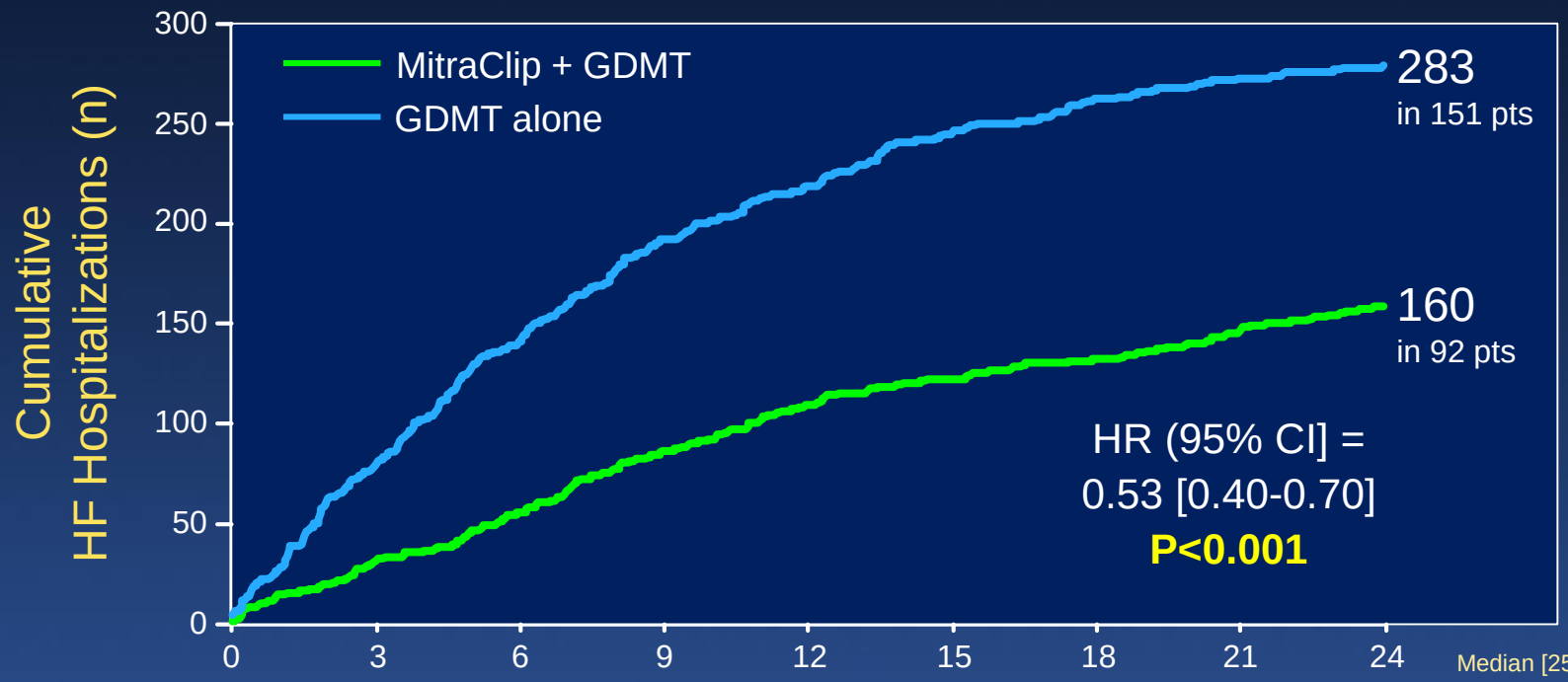
MR grade



COAPT TRIAL

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

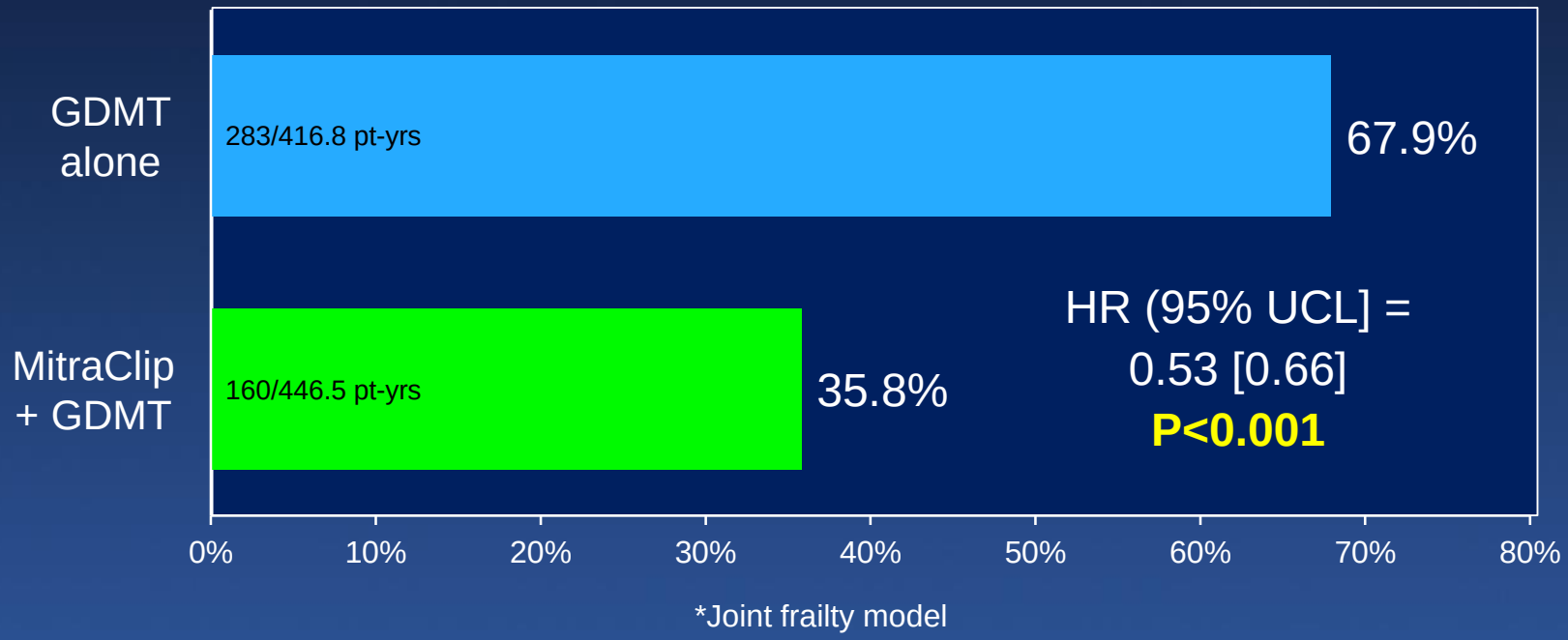
COAPT TRIAL

Primary Effectiveness Endpoint

Hospitalizations for HF within 24 months

Annualized rates of HF hospitalization*

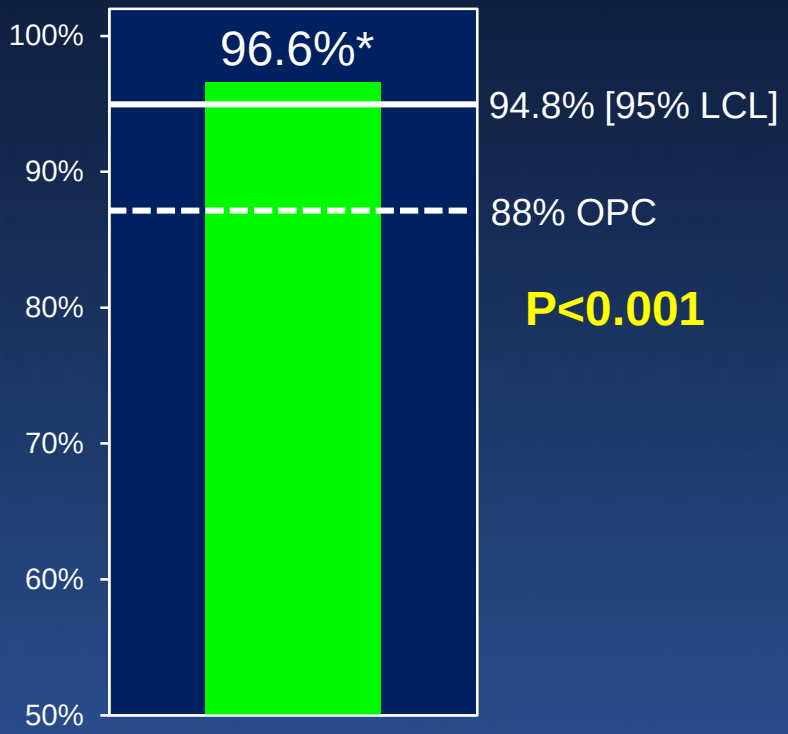
NNT (24 mo) = 3.1 [95% CI 1.9, 8.2]



*Joint frailty model

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%

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]	

[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

Powered Secondary Endpoints

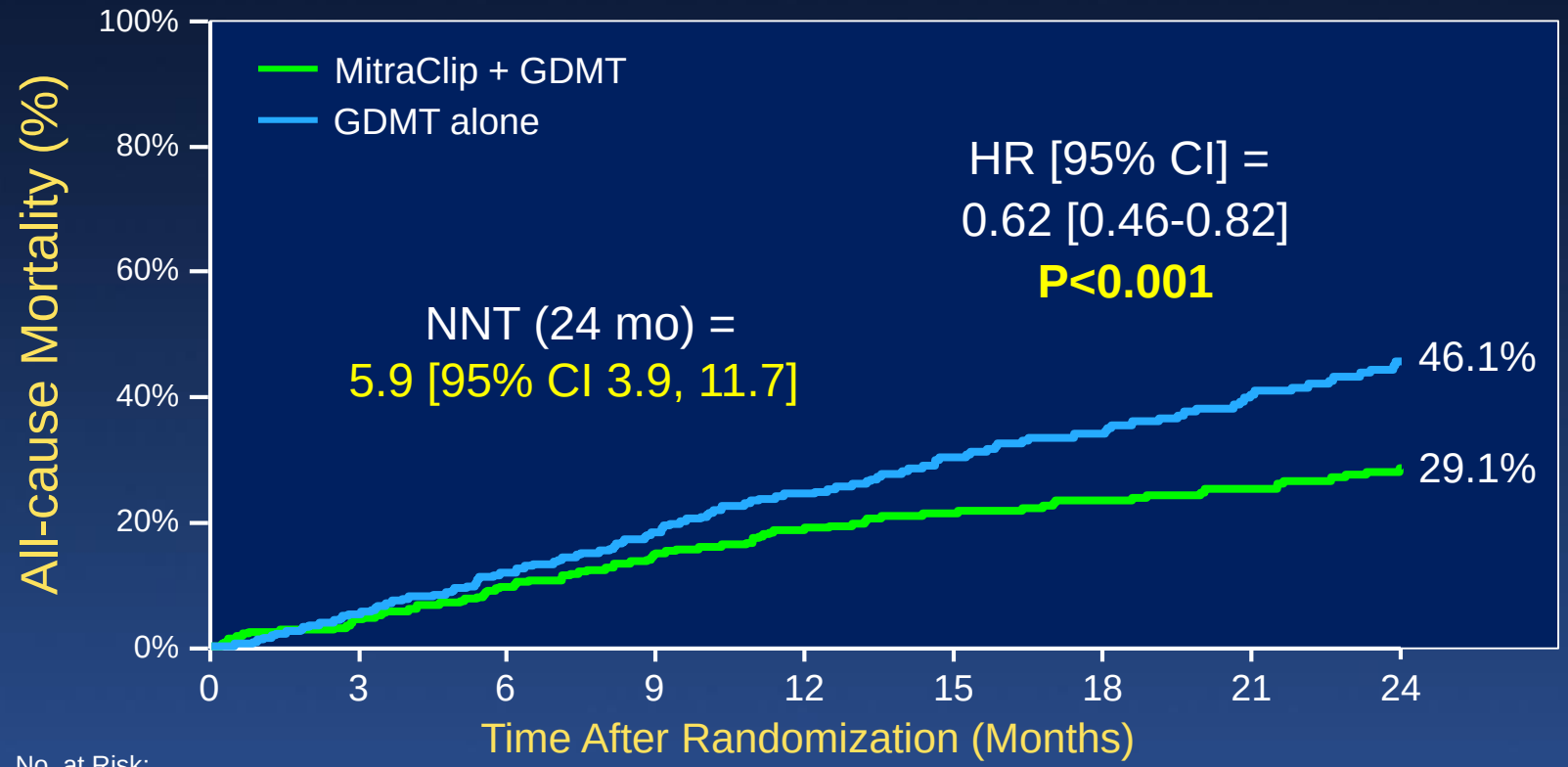
- Tested in hierarchical order[1] -

	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

COAPT TRIAL

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

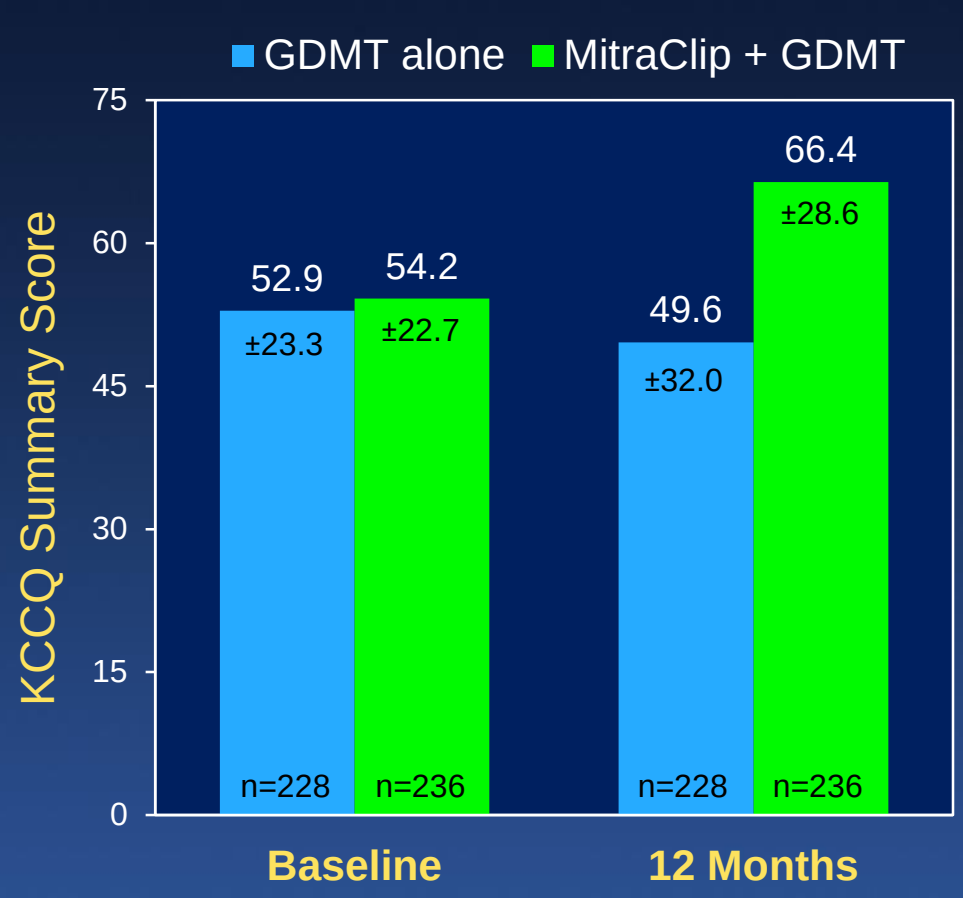
COAPT TRIAL

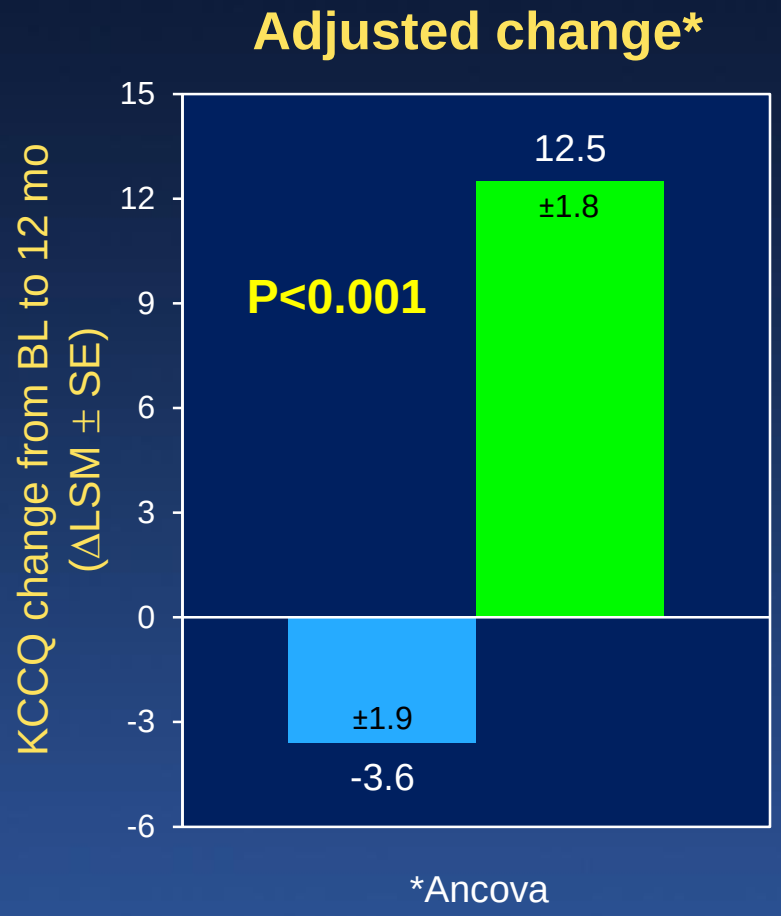
24-Month Event Rates (ii)

	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

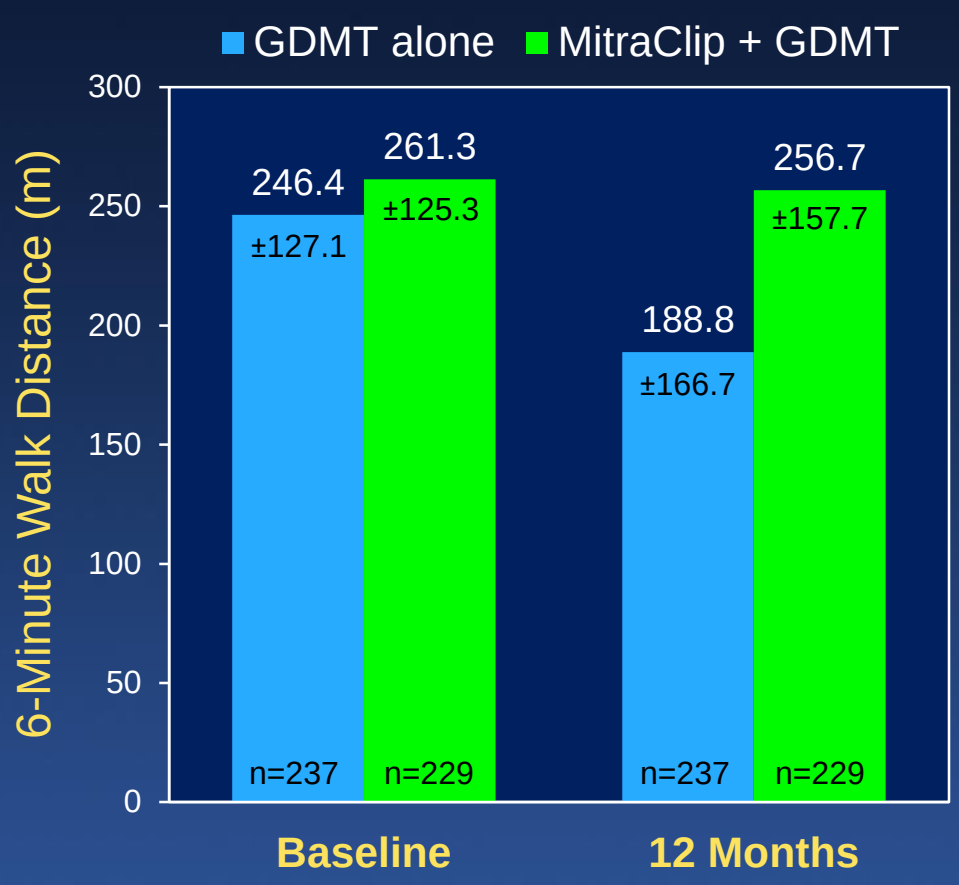
*Unplanned. Kaplan-Meier time-to-first event rates

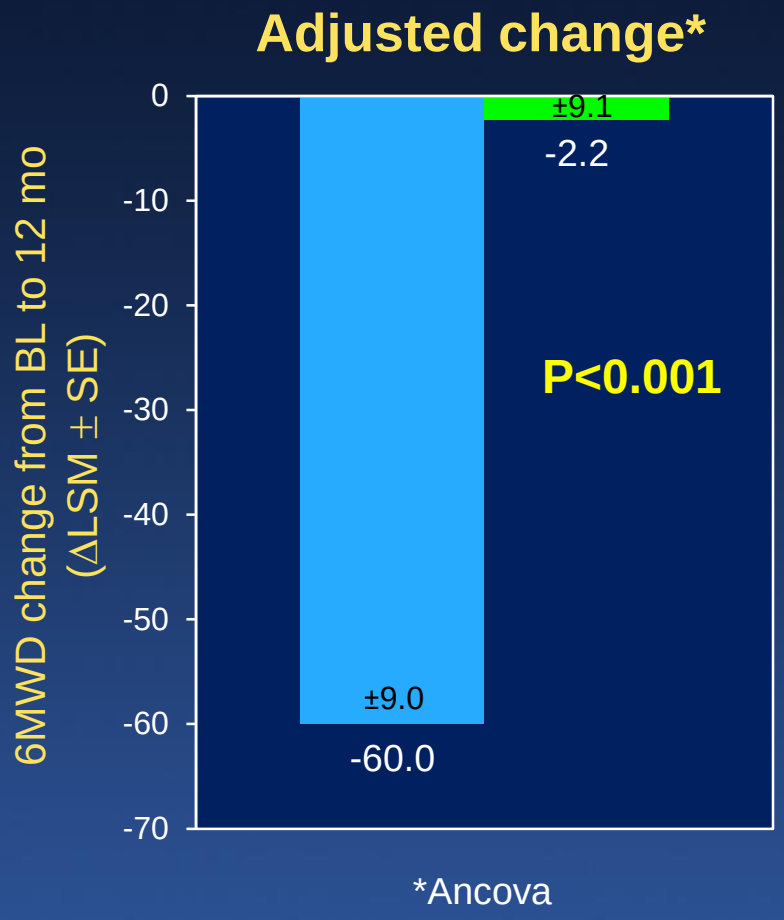
Change in KCCQ from Baseline to 12 Months





Change in 6MWD from Baseline to 12 Months





COAPT TRIAL

NYHA Functional Class

NYHA class	I	II	III	IV	HF death	P_{trend}	I or II	P-value
Baseline								
MitraClip (n=302)	0.3%	42.7%	51.0%	6.0%	-	-	43.0%	-
GDMT (n=311)	0%	35.4%	54.0%	10.6%	-		35.4%	
30 days								
MitraClip (n=283)	15.5%	60.8%	19.4%	3.5%	0.7%	<0.001	76.3%	<0.001
GDMT (n=281)	5.0%	42.7%	41.6%	9.6%	1.1%		47.7%	
6 months								
MitraClip (n=263)	19.4%	52.9%	21.3%	2.7%	3.8%	<0.001	72.2%	<0.001
GDMT (n=261)	5.4%	44.8%	38.3%	2.7%	8.8%		50.2%	
12 months								
MitraClip (n=237)	16.9%	55.3%	17.7%	2.5%	7.6%	<0.001	72.2%	<0.001
GDMT (n=232)	7.8%	41.8%	28.0%	4.7%	17.7%		49.6%	
24 months								
MitraClip (n=157)	12.1%	42.7%	21.7%	5.7%	17.8%	<0.001	54.8%	<0.001
GDMT (n=153)	5.2%	28.1%	23.5%	3.3%	39.3%		33.3%	

MR Severity (Core Lab)

MR grade	≤1+	2+	3+	4+	P_{trend}	≤2+	P-value
Baseline							
MitraClip (n=302)	-	-	49.0%	51.0%	-	-	-
GDMT (n=311)	-	-	55.3%	44.7%		-	
30 days							
MitraClip (n=273)	72.9%	19.8%	5.9%	1.5%	<0.001	92.7%	<0.001
GDMT (n=257)	8.2%	26.1%	37.4%	28.4%		34.2%	
6 months							
MitraClip (n=240)	66.7%	27.1%	4.6%	1.7%	<0.001	93.8%	<0.001
GDMT (n=218)	9.2%	28.9%	42.2%	19.7%		38.1%	
12 months							
MitraClip (n=210)	69.1%	25.7%	4.3%	1.0%	<0.001	94.8%	<0.001
GDMT (n=175)	11.4%	35.4%	34.3%	18.9%		46.9%	
24 months							
MitraClip (n=114)	77.2%	21.9%	0%	0.9%	<0.001	99.1%	<0.001
GDMT (n=76)	15.8%	27.6%	40.8%	15.8%		43.4%	

MR Severity (Core Lab)

MR grade	≤1+	2+	3+	4+	P_{trend}	≤2+	P-value
Baseline							
MitraClip (n=302)	-	-	49.0%	51.0%	-	-	-
GDMT (n=311)	-	-	55.3%	44.7%		-	
30 days							
MitraClip (n=273)	72.9%	19.8%	5.9%	1.5%	<0.001	92.7%	<0.001
GDMT (n=257)	8.2%	26.1%	37.4%	28.4%		34.2%	
6 months							
MitraClip (n=240)	66.7%	27.1%	4.6%	1.7%	<0.001	93.8%	<0.001
GDMT (n=218)	9.2%	28.9%	42.2%	19.7%		38.1%	
12 months							
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MR Severity (Core Lab)

MR grade	≤1+	2+	3+	4+	P_{trend}	≤2+	P-value
Baseline			3+-4+				
MitraClip (n=302)	-	-	49.0%	51.0%	-	-	-
GDMT (n=311)	-	-	55.3%	44.7%		-	
30 days			7.4%				
MitraClip (n=273)	72.9%	19.8%	5.9%	1.5%	<0.001	92.7%	<0.001
GDMT (n=257)	8.2%	26.1%	37.4%	28.4%		34.2%	
6 months			6.3%				
MitraClip (n=240)	66.7%	27.1%	4.6%	1.7%	<0.001	93.8%	<0.001
GDMT (n=218)	9.2%	28.9%	42.2%	19.7%		38.1%	
12 months			5.3%				
MitraClip (n=210)	69.1%	25.7%	4.3%	1.0%	<0.001	94.8%	<0.001
GDMT (n=175)	11.4%	35.4%	34.3%	18.9%		46.9%	
24 months			0.9%				
MitraClip (n=114)	77.2%	21.9%	0%	0.9%	<0.001	99.1%	<0.001
GDMT (n=76)	15.8%	27.6%	40.8%	15.8%		43.4%	

Why are the COAPT Results so Different from MITRA-FR?

Possible Reasons

	MITRA-FR (n=304)	COAPT (n=614)
Severe MR entry criteria	Severe FMR by EU guidelines: EROA >20 mm^2 or RV >30 mL/beat	Severe FMR by US guidelines: EROA >30 mm^2 or RV >45 mL/beat
EROA (mean ± SD)	31 ± 10 mm^2	41 ± 15 mm^2
LVEDV (mean ± SD)	135 ± 35 mL/m^2	101 ± 34 mL/m^2
GDMT at baseline and FU	Receiving HF meds at baseline – allowed variable adjustment in each group during follow-up per "real-world" practice	CEC confirmed pts were failing maximally-tolerated GDMT at baseline – few major changes during follow-up
Acute results: No clip / ≥3+ MR	9% / 9%	5% / 5%
Procedural complications*	14.6%	8.5%
12-mo MitraClip ≥3+ MR	17%	5%

*MITRA-FR defn: device implant failure, transf or vasc compl req surg, ASD, card shock, cardiac embolism/stroke, tamponade, urg card surg

Case 1: subsequent course

Randomized to control arm of COAPT trial on Aug 1, 2016

- Remained in NYHA Class III-IV
- Re admission of heart failure
  - March 2017, May 2017, Sept 2017.
- Begged for the Clip: Told he could cross over at 2 years
- Turned down for transplant for social reasons and patient reluctance
- Died on Sept 27, 2017. (one year 1 month after randomization)

Case 2: Subsequent Course
Enrolled in COAPT trial (randomized to clip)

- One MitraClip placed on Jan 29, 2015.
- Remained in NYHA I to II
- No heart failure admissions
- On July 2018: NYHA Class II Mild MR
- No change in medications

COAPT TRIAL

Conclusions

- In pts with HF and moderate-to-severe or severe secondary MR who remained symptomatic despite maximally-tolerated GDMT, transcatheter mitral leaflet approximation with the MitraClip was safe, provided durable reduction in MR, reduced the rate of HF hospitalizations, and improved survival, quality-of-life and functional capacity during 24-month follow-up
- As such, the MitraClip is the first therapy shown to improve the prognosis of patients with HF by reducing secondary MR due to LV dysfunction

The New York Times

Tiny Device Is a 'Huge Advance' for Treatment of Severe Heart Failure

A clip used to repair damaged heart valves sharply reduced deaths among patients with a grim prognosis.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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*

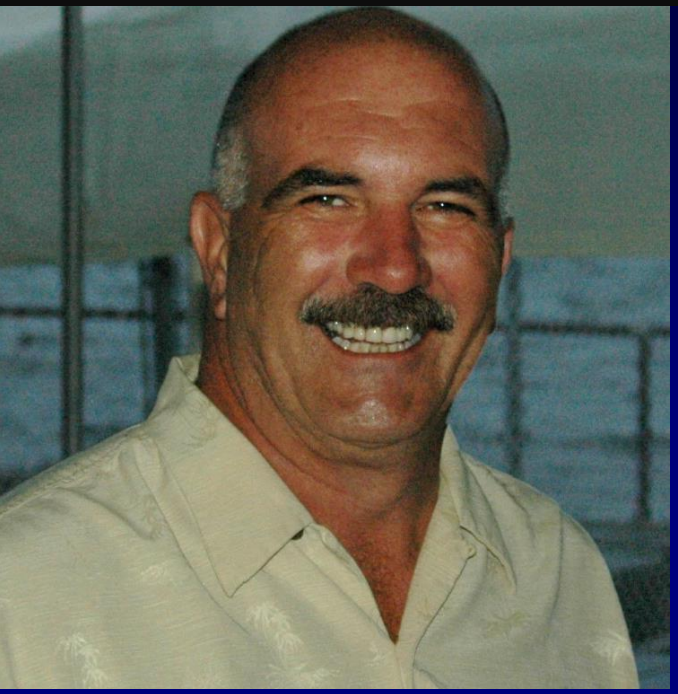
CEDARS-SINAI MEDICAL CENTER

Implications

- In patients with severe secondary MR, with suitable anatomy, despite maximally tolerated GDMT, MitraClip should be considered as the first line treatment irrespective of the surgical risk.

- All other surgical or transcatheter valve repair or replacement options should be evaluated against MitraClip

Gerard Powers: Clinical Specialisty



Patients in the Clinical Trial

Ferolyn Powell, CEO of Evalve

July 2, 1962 to Mar 13, 2015

You shall be missed, but never forgotten

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