Future of the MitraClip
After the COAPT Trial

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Icahn School of Medicine at Mount Sinai, NY
and the Cardiovascular Research Foundation

Mount Sinai Heart

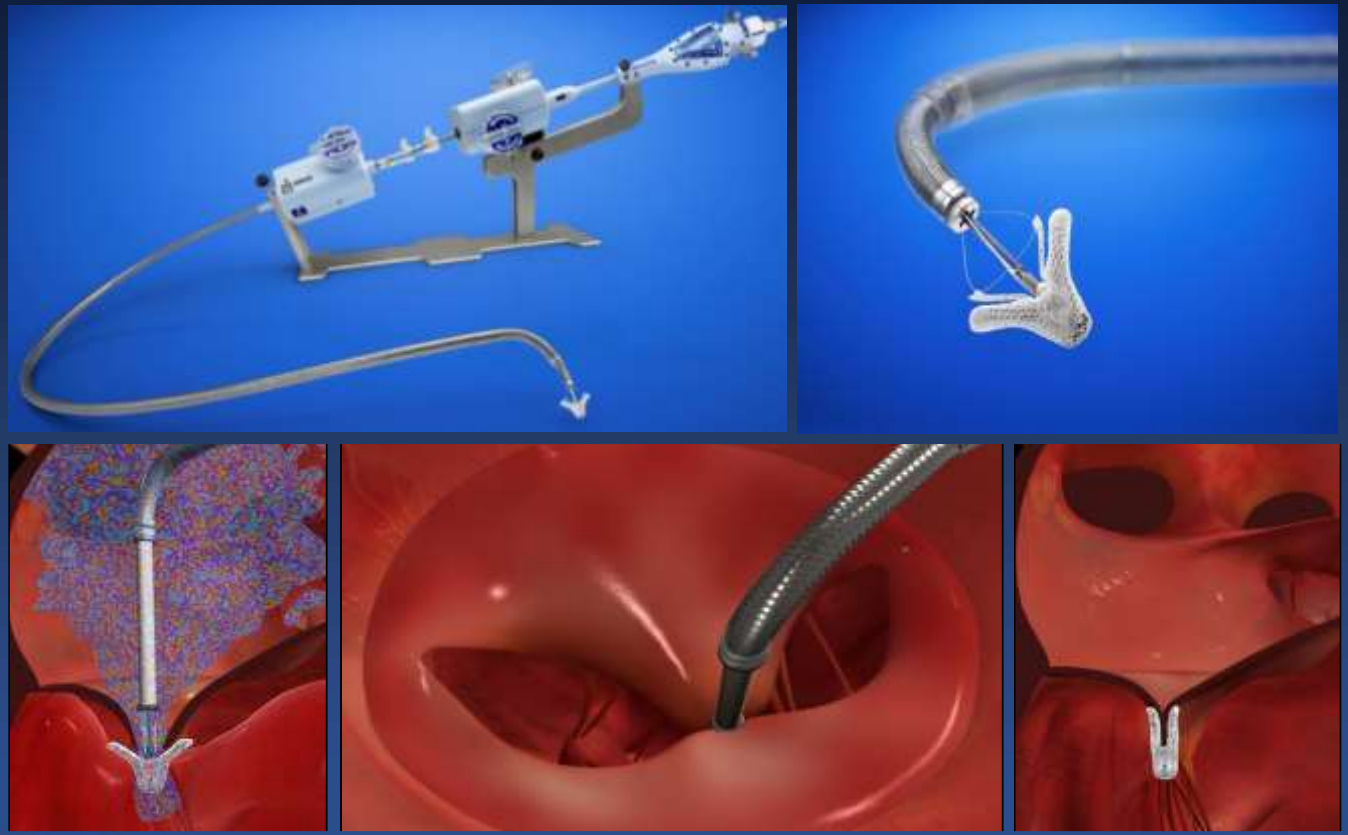
Cardiovascular Research Foundation®

Relevant Disclosures

Consulting fees from Neovasc, Valfix, Gore

Equity/options/consulting fees from Ancora

MitraClip System and Implant



EVEREST II Randomized Clinical Trial

279 patients enrolled at 37 sites

Severe MR (3+ or 4+)

73% DMR, 27% FMR

Specific anatomical criteria

Randomize 2:1

Device Group
MitraClip system
N=184

Control Group
Surgical repair or replacement
N=95

Echocardiography core lab and clinical follow-up
Baseline, 30 days, 6 months, 1 year, 18 months, and annually through 5 years

Mount Sinai Heart

Feldman T et al. NEJM 2011;364:1395-406

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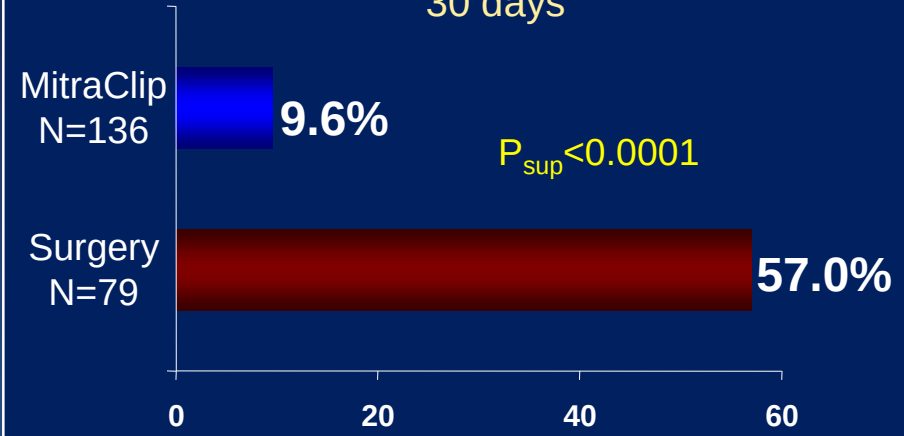
EVEREST II: 279 pts with 3+/4+ MR randomized 2:1 to MitraClip vs. Surgical Repair

Primary Endpoints (per protocol cohort)

Safety†

Major Adverse Events

30 days



† Death, major stroke, reoperation of MV, urgent/emergent CV surgery, MI, renal failure, deep wound infection, sepsis, ventilation >48 hrs, new permanent AF, GI complication requiring surgery, transfusion ≥2U

Effectiveness‡

Clinical Success Rate

12 months

‡ Freedom from death, MV surgery or reoperation for MV dysfunction, or MR >2+ at 12 months

Mount Sinai Heart

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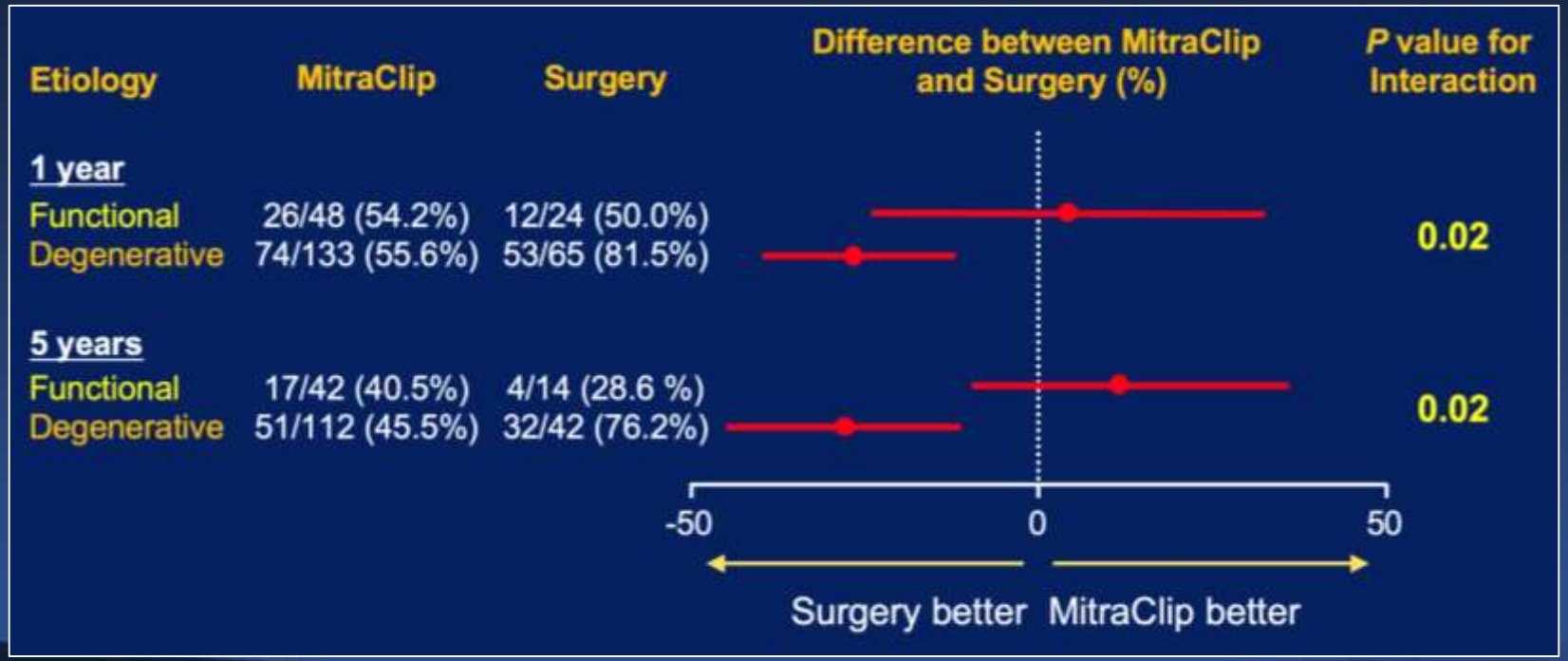
EVEREST II: Primary EP at 1 and 5 Years
- DMR (73%) vs. FMR (27%) -
(Freedom from Death, MV Surgery, or 3+ or 4+ MR): ITT



Mount Sinai Heart

Feldman T et al. NEJM 2011;364:1395-406
Feldman T et al. *JACC* 2015;66:2844–54

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Primary (Degenerative) MR

Mis-aligned and thickened leaflets allows backflow of blood into the left atrium

Surgical leaflet repair: Excellent outcomes at centers of excellence

Surgical MV repair is the standard of care!

Pts are typically referred for surgery when MR reaches 3-4+, left ventricular size has increased, functional status has become impaired, and the surgical risk is acceptable

FDA MitraClip Approval

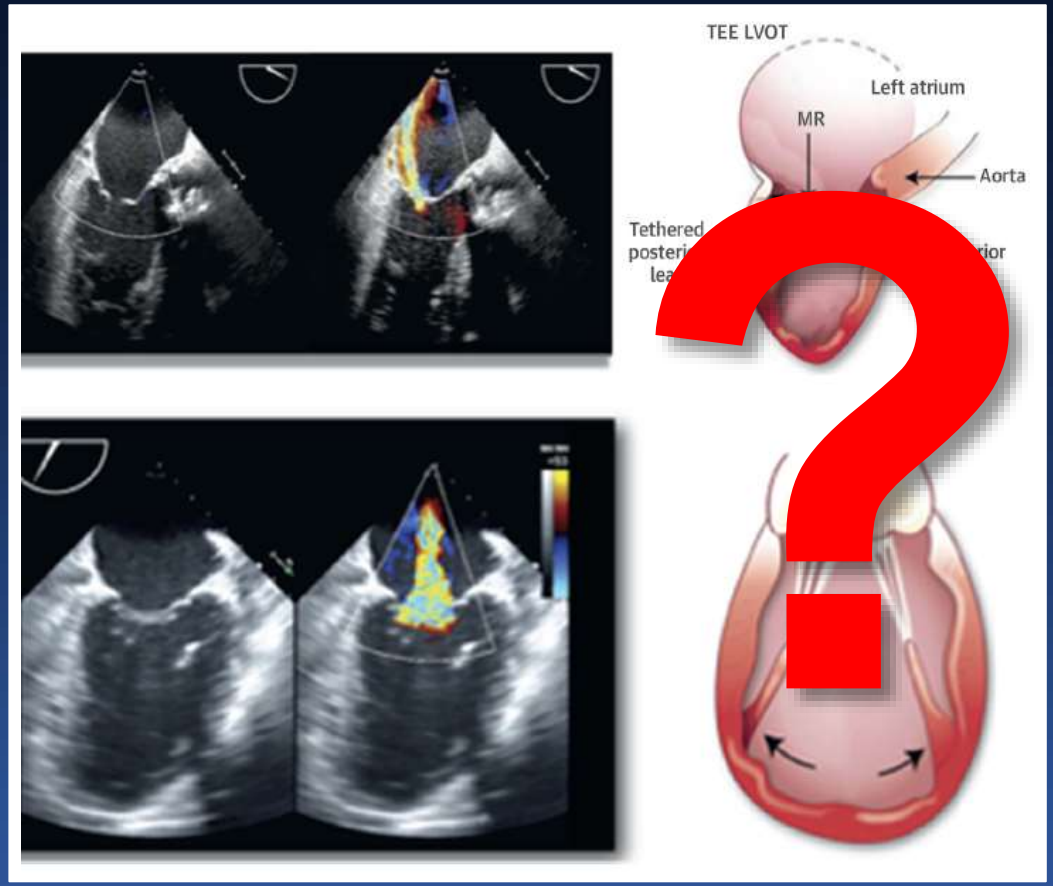
October 24th, 2013

The MitraClip is approved for treatment of patients with 3+-4+ primary (degenerative) MR who are at “prohibitive risk” for mitral valve surgery and are likely to benefit from MR reduction

Secondary (Functional) MR: The disease is the LV!

Ischemic cardiomyopathy

Idiopathic dilated cardiomyopathy

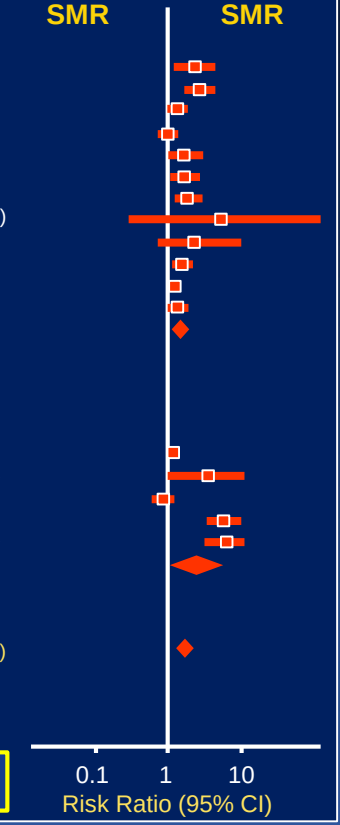


Asgar, Mack, Stone. J Am Coll Cardiol 2015;65:1231–48

Natural History of Functional MR

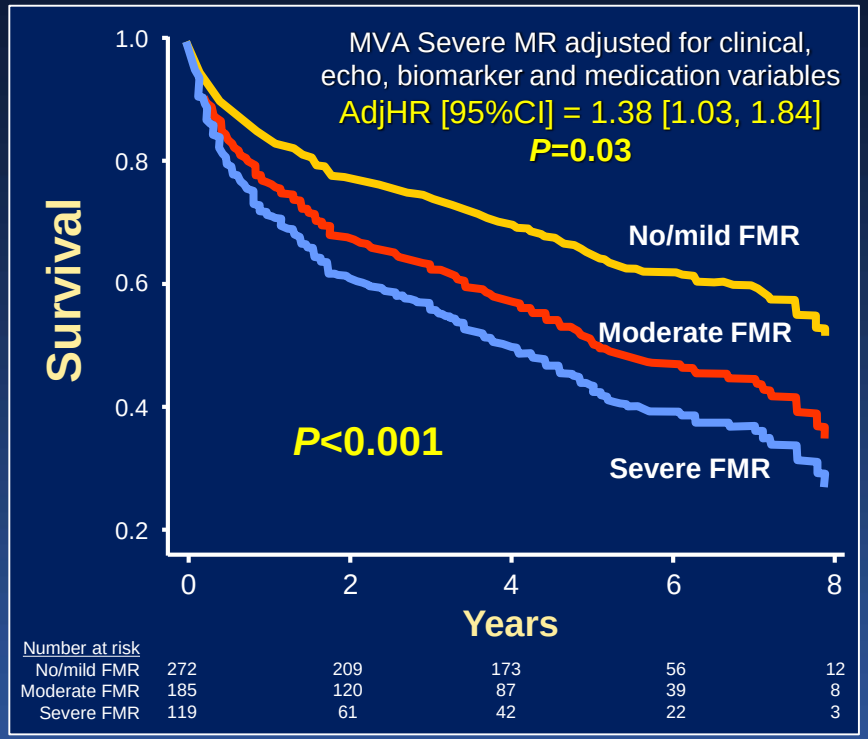
Meta-analysis, 17 studies, 26,359 pts

Source	Log Risk Ratio (SE)	Risk Ratio (SE)
SMR Present vs. Absent at Echocardiography		
Agricola et al,[26] 2011	0.8538 (0.3182)	2.35 (1.26-4.38)
Aronson et al,[8] 2006	1.0188 (0.1977)	2.77 (1.88-4.08)
Barra et al,[27] 2012	0.3507 (0.1638)	1.42 (1.03-1.96)
Calafiore et al,[7] 2008	0.0296 (0.1226)	1.03 (0.81-1.31)
Engström et al,[30] 2010	0.5365 (0.2636)	1.71 (1.02-2.87)
Faris et al,[31] 2002	0.5878 (0.2513)	1.80 (1.10-2.95)
Grigioni et al,[2] 2001	0.6313 (0.2165)	1.88 (1.23-2.87)
MacHaalany et al,[43] 2014	1.8183 (1.5567)	6.16 (0.29-130.24)
Nesković et al,[46] 1999	0.9060 (0.6158)	2.47 (0.74-8.27)
Pastorius et al,[48] 2007	0.4511 (0.1371)	1.57 (1.20-2.05)
Trichon et al,[53] 2003	0.2070 (0.0433)	1.23 (1.13-1.34)
Upadhyay et al,[55] 2015	0.2852 (0.1404)	1.33 (1.01-1.75)
Subtotal (95% CI)		1.56 (1.31-1.85)
Heterogenity: τ^2=0.05; χ^2=33.07, (*P*<0.001); I^2=67%		
Test for overall effect: Z=5.08 (*P*<0.001)		
SMR Present vs. Absent at Ventriculography		
Hickey et al,[36] 1988	0.2231 (0.0746)	1.25 (1.08-1.45)
Lehmann et al,[41] 1992	1.3083 (0.6189)	3.70 (1.10-12.45)
Mallidi et al,[9] 2004	-0.0429 (0.1420)	0.96 (0.73-1.27)
Pellizzon et al,[3] 2004	1.7297 (0.2303)	5.64 (3.59-8.86)
Tcheng et al,[52] 1992	1.8160 (0.2947)	6.15 (3.45-10.95)
Subtotal (95% CI)		2.58 (1.29-5.17)
Heterogenity: τ^2=0.54; χ^2=73.55, (*P*<0.001); I^2=95%		
Test for overall effect: Z=2.67 (*P*<0.008)		
Total (95% CI)		1.79 (1.47-2.18)
Heterogenity: τ^2=0.12; χ^2=107.97, (*P*<0.001); I^2=85%		
Test for overall effect: Z=5.71 (*P*<0.001)		
Test for subgroup differences: Z=1.89 (*P*=0.17) I^2=47.2%		



RR for Death 1.79 [1.47-2.18], *p*<0.001

Prospective study of 576 pts with HFrEF; severe FMR in 21%, mod FMR in 32%



Sannino A et al. JAMA Cardiol. 2017;2:1130-9
Goliasch G et al. *EHJ* 2018;39:39-46

The MITRA-FR Trial

304 pts with SMR due to LV dysfunction with LVEF 15-40%, NYHA II-IVa, hospitalization for HF within the previous 12 mos, not eligible for mitral surgery

MR defined by EU “severe” criteria as EROA >20 mm² or RVol >30 mL/beat

Both groups with “real-world” HF meds (not maximally-tolerated GDMT)

Randomize 1:1
at 37 French centers

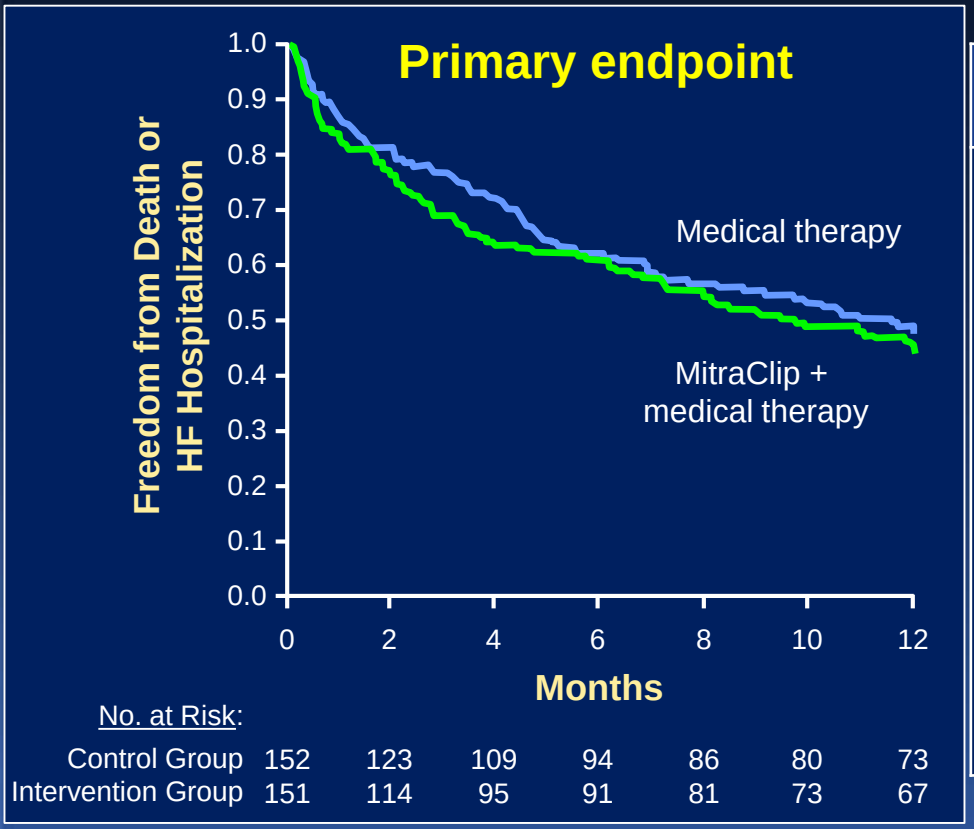
MitraClip + MT
N=152

MT alone
N=152

Primary endpoint: Freedom from death or HF hospitalizations through 12 months

Obadia JF et al. N Engl J Med. 2018;379:2297-306

MITRA-FR: 12-Month Outcomes



	MitraClip + MT	MT alone	OR [95% CI] or HR [95% CI]*	*P* value
1° EP: Death or HF hosp	54.6%	51.3%	1.16 [0.73–1.84]	0.53
Death	24.3%	22.4%	1.11 [0.69–1.77]*	0.65
CV death	21.7%	20.4%	1.09 [0.67–1.78]*	0.74
HF hosp	48.7%	47.4%	1.13 [0.81–1.56]*	0.59
MACE*	56.6%	51.3%	1.22 [0.89–1.66]*	–

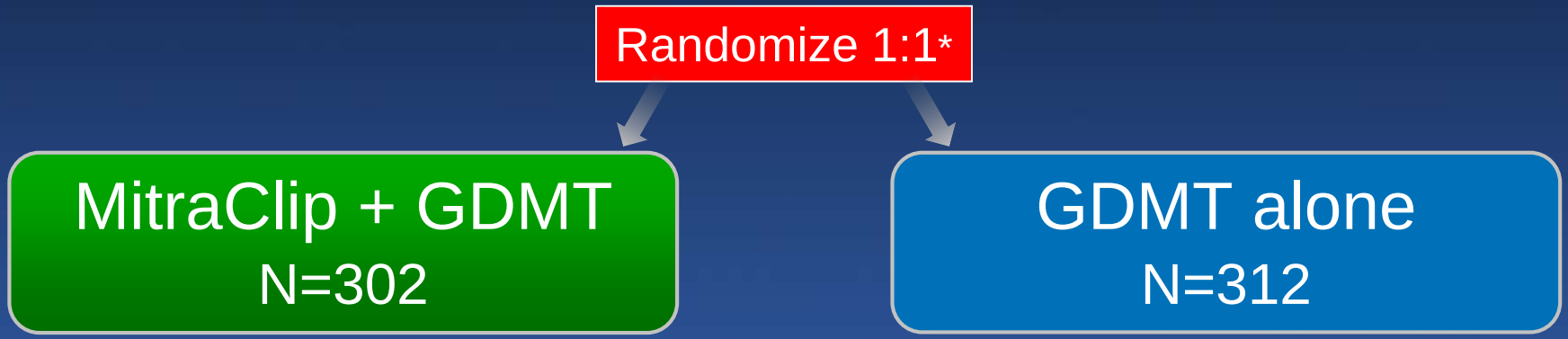
* MACE = Death, MI, CVA, HF hosp

Obadia JF et al. N Engl J Med. 2018;379:2297-306

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 614 patients with heart failure and moderate-to-severe (3+) or severe (4+) secondary MR who remained symptomatic despite maximally-tolerated GDMT

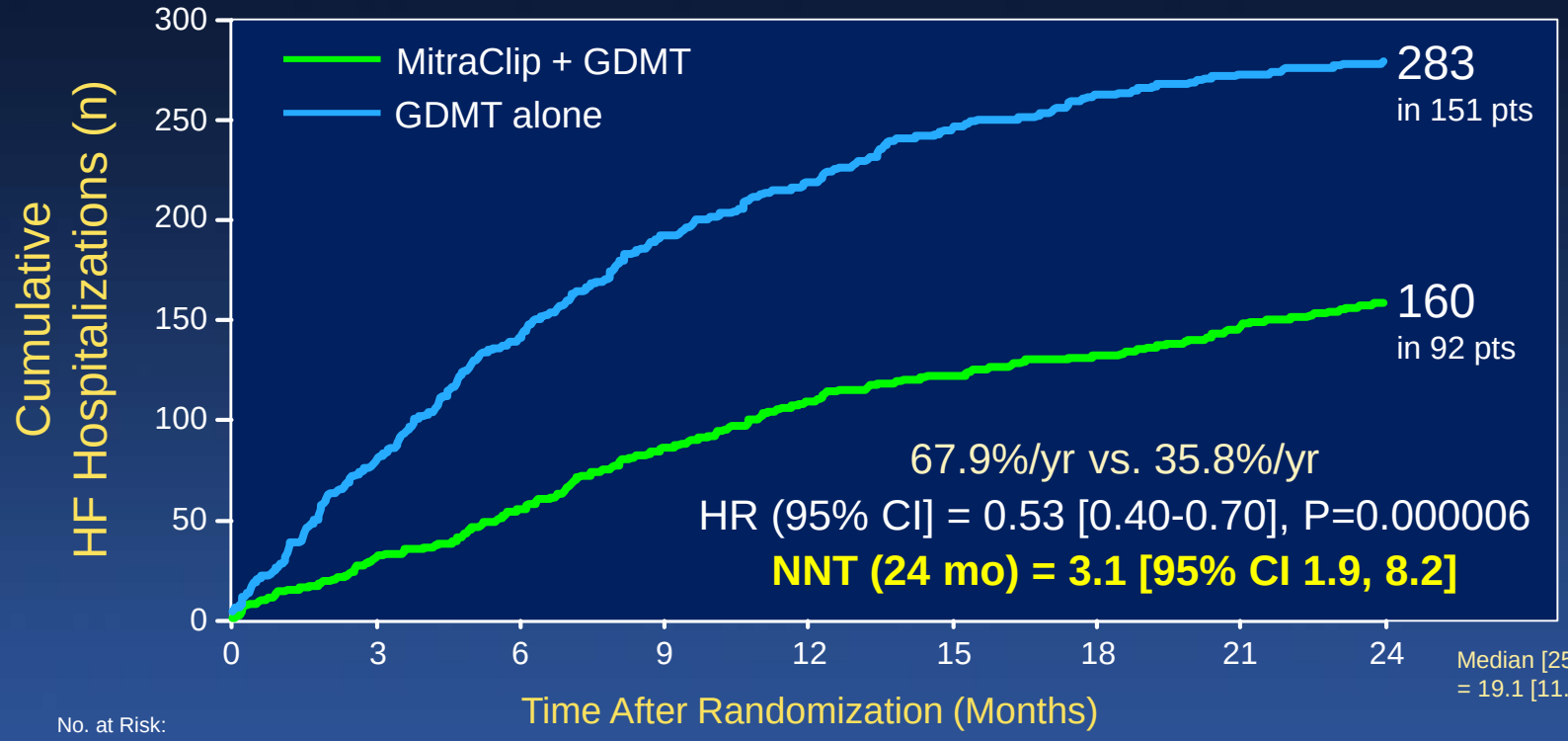


*Stratified by cardiomyopathy etiology (ischemic vs. non-ischemic) and site

Stone GW et al. N Engl J Med. 2018;379:2307-18

Primary Effectiveness Endpoint

All Hospitalizations for HF within 24 months



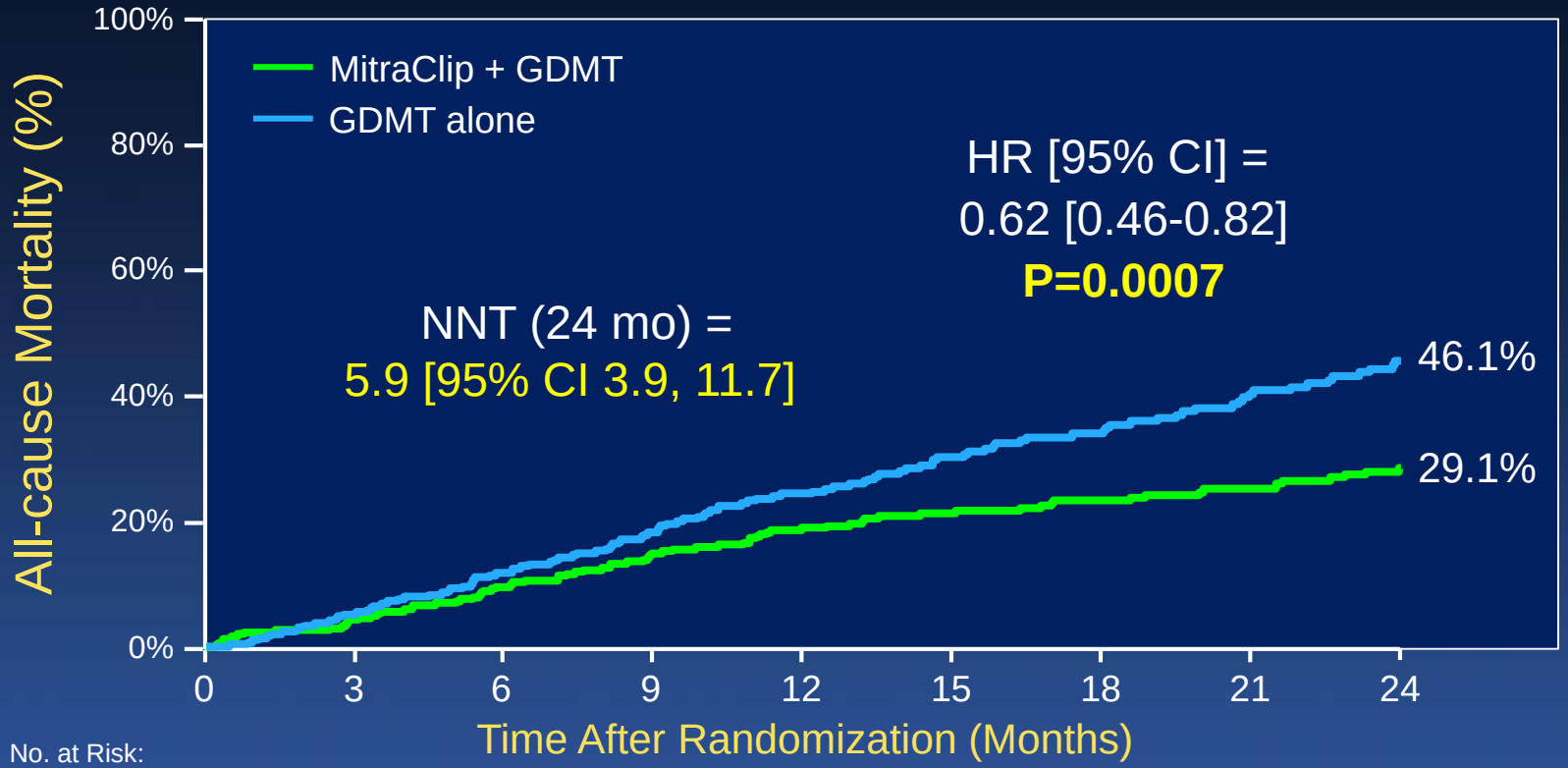
Median [25%, 75%] FU = 19.1 [11.9, 24.0] mos

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

All-cause Mortality

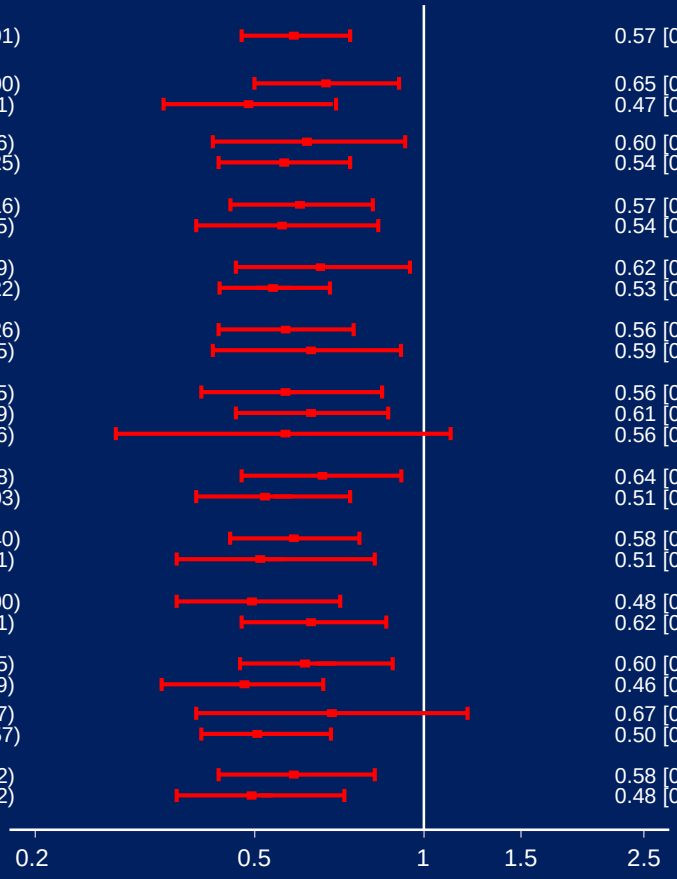


No. at Risk:									
MitraClip + GDMT	302	286	269	253	236	191	178	161	124
GDMT alone	312	294	271	245	219	176	145	121	88

Stone GW et al. N Engl J Med. 2018;379:2307-18

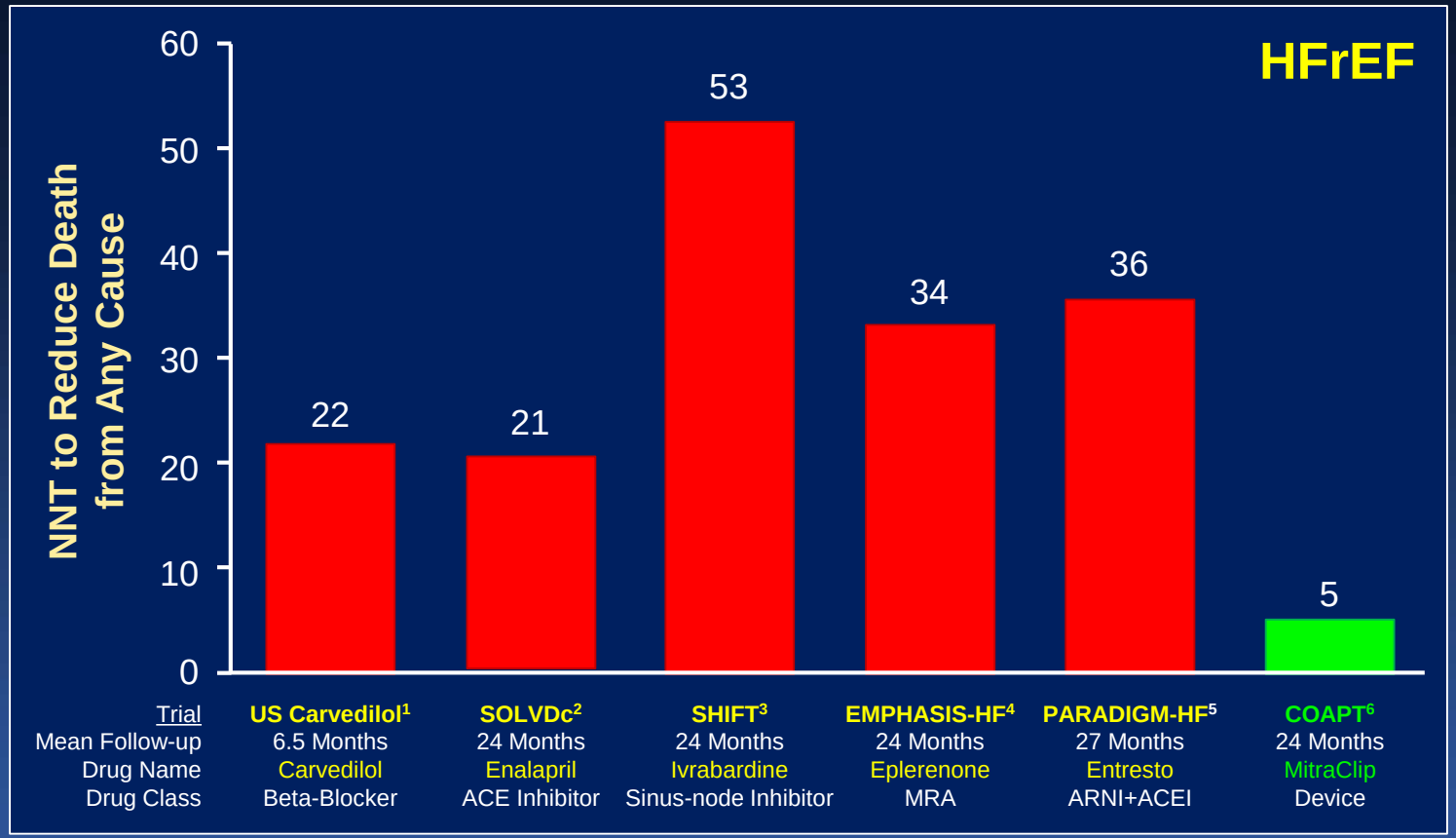
24-Month Death or HF Hospitalization

Subgroup	MitraClip + GDMT	GDMT alone	HR [95% CI]	P [Int]
All patients	45.7% (129)	67.9% (191)	0.57 [0.45, 0.71]	
Age (median)				
≥74 years (n=317)	52.1% (78)	70.2% (100)	0.65 [0.48, 0.88]	0.13
<74 years (n=297)	37.8% (51)	65.3% (91)	0.47 [0.33, 0.66]	
Sex				
Female (n=221)	43.2% (39)	59.4% (66)	0.60 [0.40, 0.89]	0.76
Male (n=393)	47.1% (90)	73.0% (125)	0.54 [0.41, 0.71]	
Etiology of cardiomyopathy				
Ischemic (n=373)	48.1% (84)	70.0% (116)	0.57 [0.43, 0.76]	0.79
Non-ischemic (n=241)	41.1% (45)	65.2% (75)	0.54 [0.37, 0.78]	
Prior CRT				
Yes (n=224)	50.2% (55)	68.4% (69)	0.62 [0.44, 0.89]	0.54
No (n=390)	42.9% (74)	67.4% (122)	0.53 [0.39, 0.71]	
HF hospitalization within the prior year				
Yes (n=407)	44.7% (86)	67.9% (126)	0.56 [0.42, 0.73]	0.79
No (n=207)	47.6% (43)	67.8% (65)	0.59 [0.40, 0.86]	
Baseline NYHA class				
I or II (n=240)	41.1% (50)	66.9% (65)	0.56 [0.39, 0.81]	0.92
III (n=322)	46.6% (67)	65.3% (99)	0.61 [0.44, 0.83]	
IV (n=51)	68.3% (12)	84.4% (26)	0.56 [0.28, 1.12]	
STS replacement score				
≥8% (n=262)	54.1% (65)	71.4% (88)	0.64 [0.46, 0.88]	0.41
<8% (n=352)	39.2% (64)	65.0% (103)	0.51 [0.37, 0.70]	
Surgical risk status*				
High (n=423)	49.7% (95)	71.5% (140)	0.58 [0.45, 0.75]	0.69
Not high (n=188)	35.8% (32)	58.7% (51)	0.51 [0.33, 0.80]	
Baseline MR grade				
3+ (n=320)	37.5% (51)	65.3% (100)	0.48 [0.34, 0.67]	0.29
4+ (n=293)	53.4% (78)	71.4% (91)	0.62 [0.45, 0.83]	
Baseline LVEF				
≥30% (median; n=301)	44.1% (62)	61.2% (85)	0.60 [0.43, 0.84]	0.32
<30% (median; n=274)	46.4% (56)	77.8% (99)	0.46 [0.33, 0.64]	
>40% (n=103)	49.7% (22)	56.2% (27)	0.67 [0.38, 1.17]	0.31
≤40% (n=472)	44.2% (96)	71.9% (157)	0.50 [0.39, 0.65]	
Baseline LVEDV (median)				
≥181 mL (n=288)	48.9% (43)	68.0% (92)	0.58 [0.42, 0.80]	0.42
<181 mL (n=287)	41.5% (54)	69.5% (92)	0.48 [0.34, 0.67]	



KM time-to-first event rates
*Central eligibility committee assessment

Number Needed to Treat (NNT) to Prevent 1 Death



1. Packer M et al. NEJM 1996;334:1349-1355; 2. SOLVD Investigators. NEJM 1991;325:293-302; 3. Swedberg K et al. Lancet 2010;376:1988;
4. Zannad F et al. NEJM 2011;364:11-21; 5. McMurray JJV et al. NEJM 2014;371:993-1004; 6. Stone GW et al. NEJM 2018;379:2307-18.

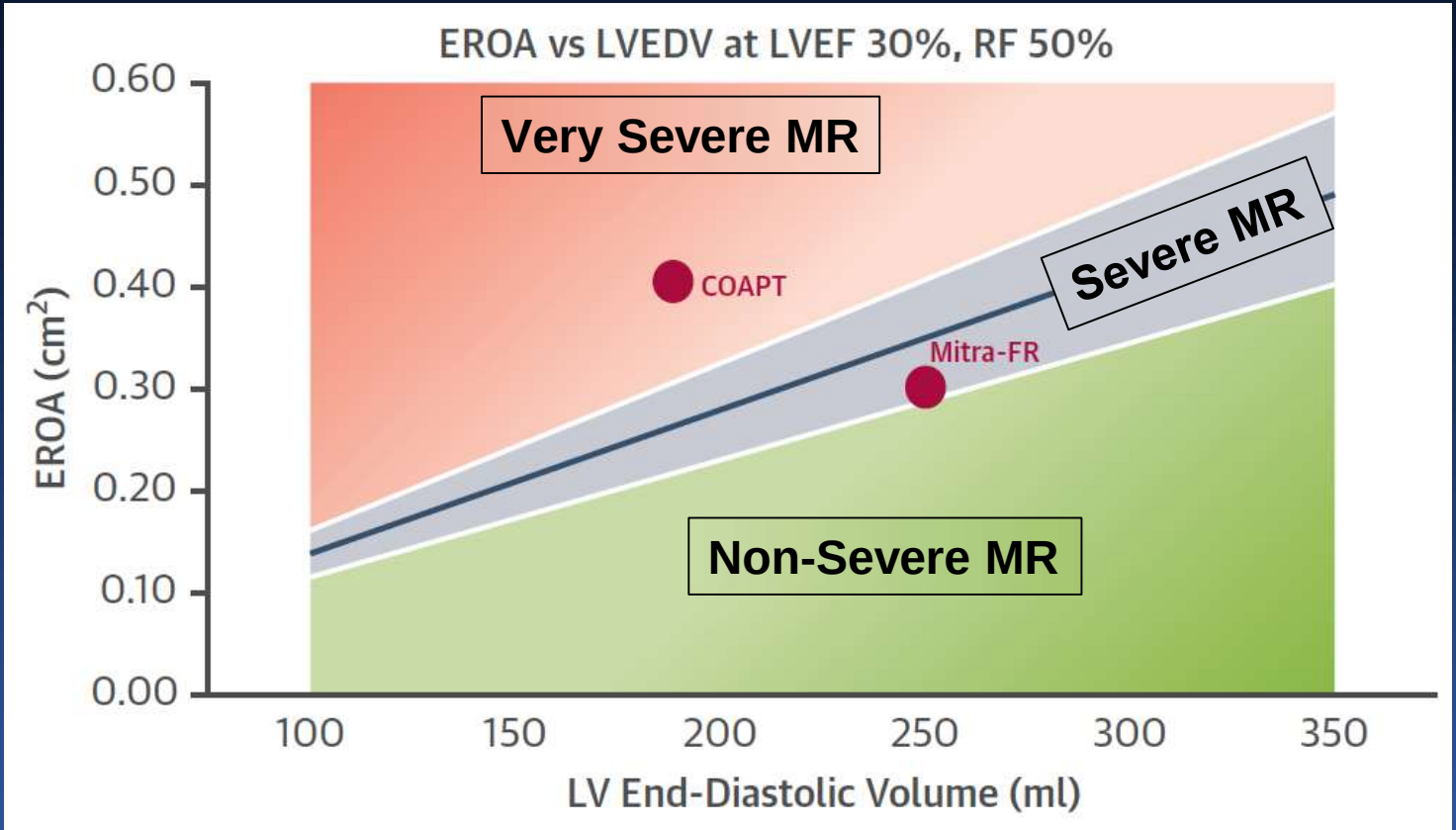
Why are the COAPT Results so Different from MITRA-FR?

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 or PSVFR or other
EROA (mean ± SD)	31 ± 10 mm^2	41 ± 15 mm^2
LVEDV (mean ± SD)	135 ± 35 mL/m^2	101 ± 34 mL/m^2

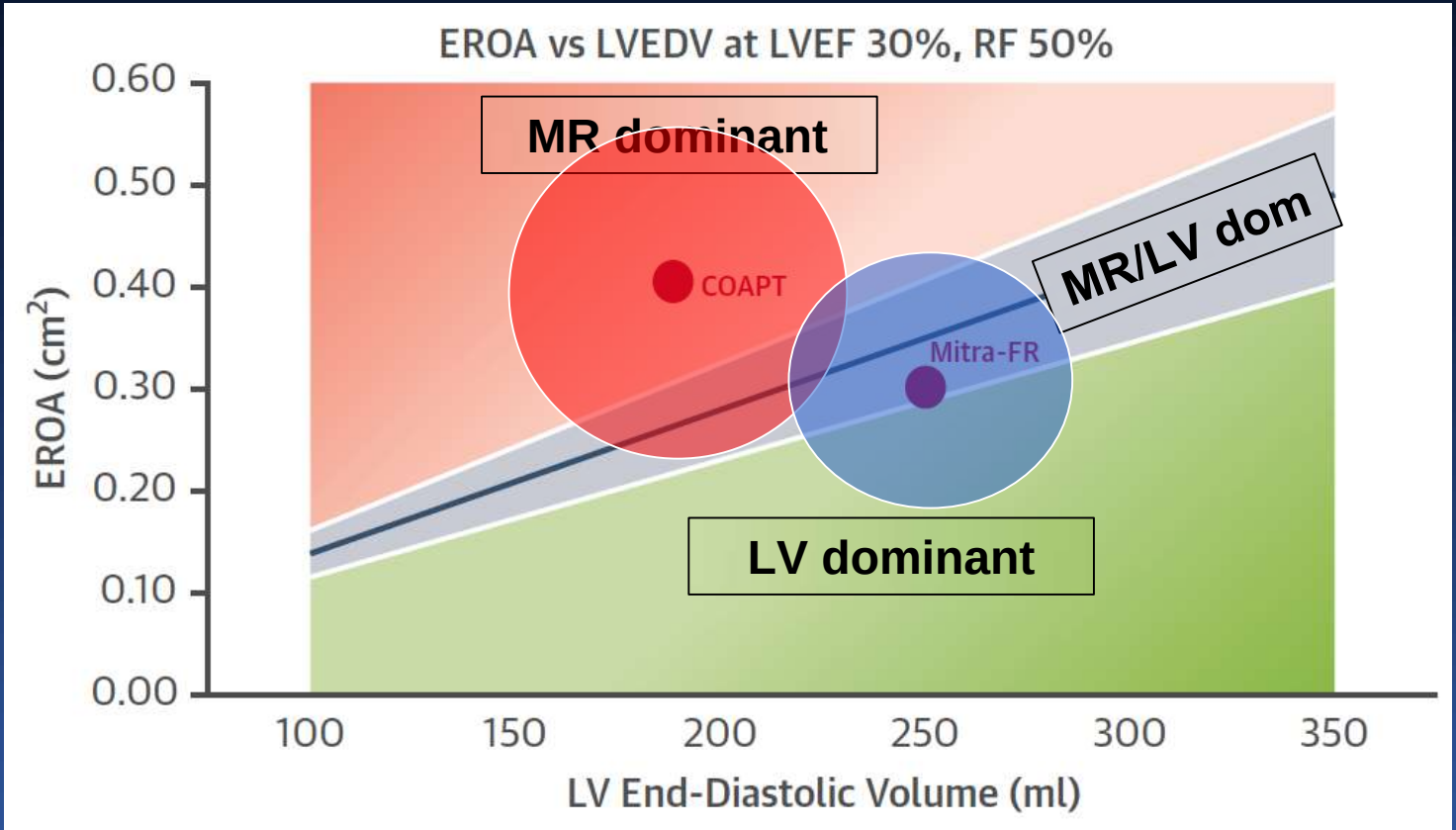
*MITRA-FR defn: device implant failure, transf or vasc compl req surg, ASD, card shock, cardiac embolism/stroke, tamponade, urg card surg

Proportionate vs. Disproportionate MR



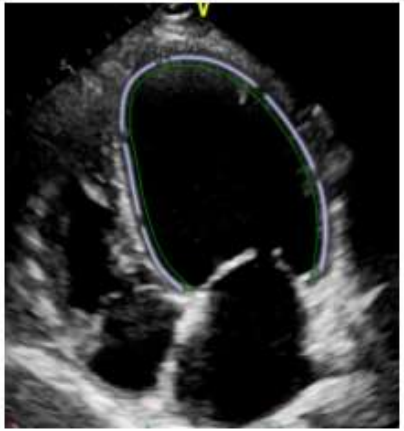
Grayburn PA et al. JACC CV Im 2019;12:353–62

Proportionate vs. Disproportionate MR

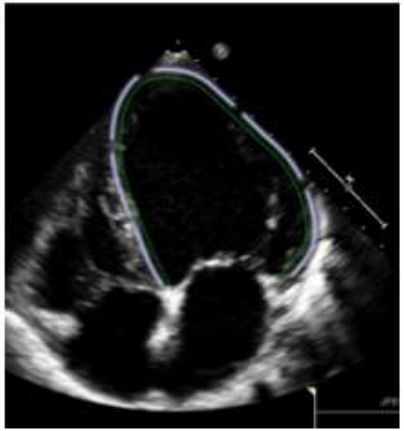


Grayburn PA et al. JACC CV Im 2019;12:353–62

3 Patients with EROA of 30 mm^2



LVEF 22%
LVEDV 310 mL
GLS -6.8%



LVEF 36%
LVEDV 197 mL
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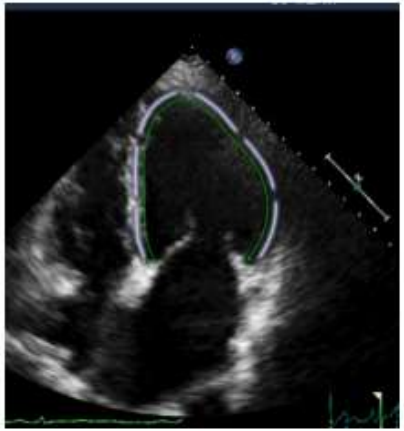


LVEF 60%
LVEDV 140 mL
GLS -20.3%

LVAD, transplant, hospice

Spectrum of LV dysfunction

MR correction likely to be beneficial

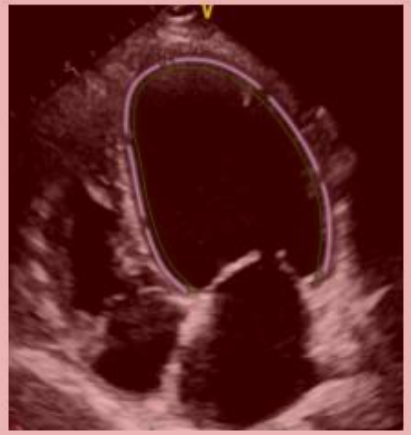
LVEF, LV size, LV geometry
Severely abnormal

LVEF, LV size, LV geometry
Mild-to-moderately abnormal

LVEF, LV size, LV geometry
Normal

3 Patients with EROA of 30 mm^2

MITRA-FR



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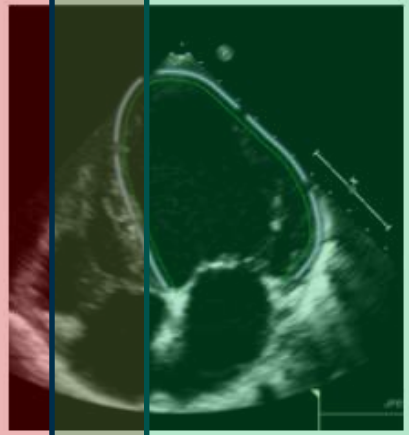

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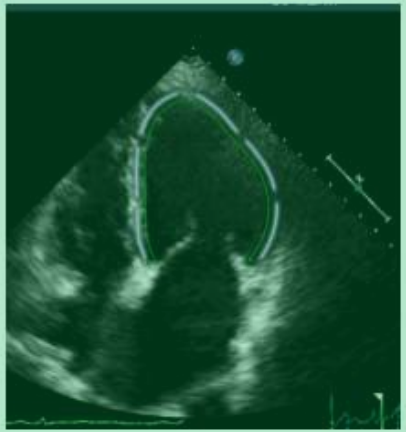

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COAPT

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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

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

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Acute results: No clip / ≥3+ MR	9% / 9%	5% / 5%
Procedural complications*	14.6%	8.5%
12-mo MitraClip MR ≤2+ / ≥3+	83% / 17%	95% / 5%

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

March 14th, 2019

FDA approves MitraClip for treatment of select patients with severe secondary MR who remain symptomatic despite GDMT

Label: The MitraClip™ NTR/XTR Clip Delivery System, when used with maximally tolerated guideline-directed medical therapy (GDMT), is indicated for the treatment of symptomatic, moderate-to-severe or severe secondary (or functional) mitral regurgitation (MR; MR ≥ Grade III per American Society of Echocardiography criteria) in patients with a left ventricular ejection fraction (LVEF) ≥ 20% and ≤ 50%, and a left ventricular end systolic dimension (LVESD) ≤ 70 mm whose symptoms and MR severity persist despite maximally tolerated GDMT as determined by a multidisciplinary heart team experienced in the evaluation and treatment of heart failure and mitral valve disease.

Implications of the COAPT Trial

- COAPT and MITRA-FR provide complementary guidance for pt selection, demonstrating which pts with HF and secondary MR are likely and unlikely to benefit from MR reduction
- The FDA has approved the MitraClip for pts with HF and secondary MR meeting COAPT criteria; strict reliance to these criteria should allow duplication of the COAPT results in the “real world” (and avoid over-treatment)
- Ongoing and future trials investigating surgical and transcatheter MV repair and replacement techniques and devices in HF pts with secondary MR who meet COAPT criteria must include the MitraClip as an active control arm