Optimal Candidate for MitraClip in Heart Failure – New Insights from COAPT

Susheel Kodali, MD

Director, Structural Heart & Valve Center

Avanessians Associate Professor of Medicine

Columbia University Medical Center

New York Presbyterian Hospital

Disclosure Statement of Financial Interest

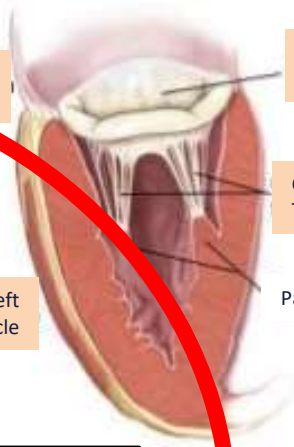
Susheel K. Kodali, MD

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
• Consultant	• Admedus, Dura Biotech
• SAB	• Thubrikar Aortic Valve, Inc, Dura Biotech, Supira, MID, Admedus, TriFlo Medical

Mitral Regurgitation: Not a single disease entity

Mitral Regurgitation



Functional Mitral Regurgitation (FMR)

LV Dysfunction
Dilated Annulus
(Non-ischemic or ischemic dilated cardiomyopathy)

Etiologies

LA Dysfunction
Dilated Annulus
(Chronic atrial fibrillation, hypertension)

Loss of leaflet coapation due to:
- annular enlargement
- Papillary muscle displacement causing leaflet tethering/tenting

Degenerative Mitral Regurgitation (DMR)

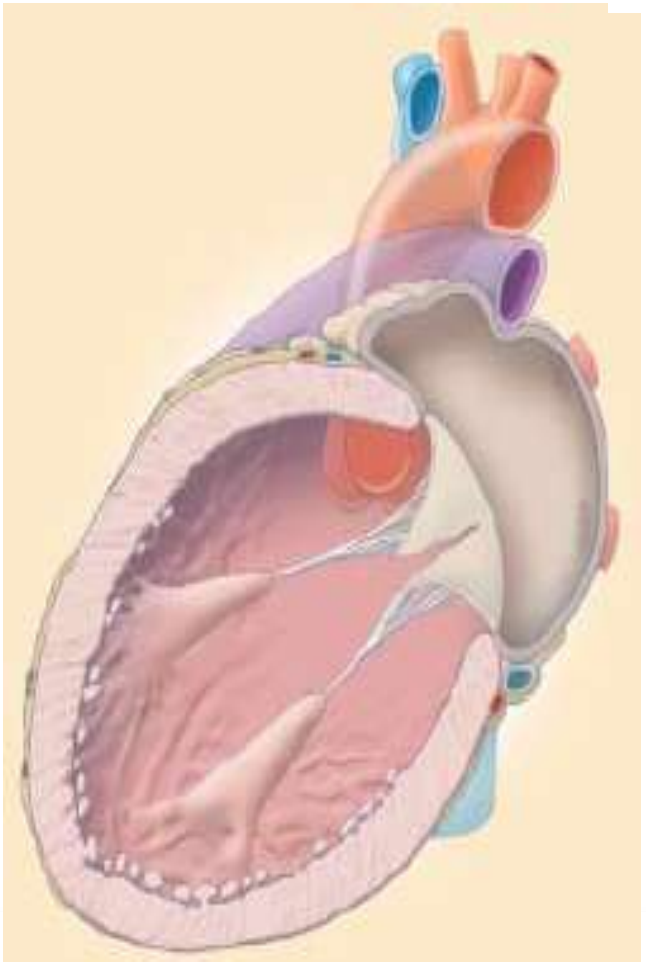
Etiologies:
- Advanced Barlow's Disease
- **Fibroelastic deficiency (affects leaflets and annulus)**

Leaflet prolapse due to:
- Leaflet deformities or lesions
- Ruptured/ elongated chordae
- Papillary muscle rupture

Benjamin MM et al. Curr Cardiol Rep 2014;16:517

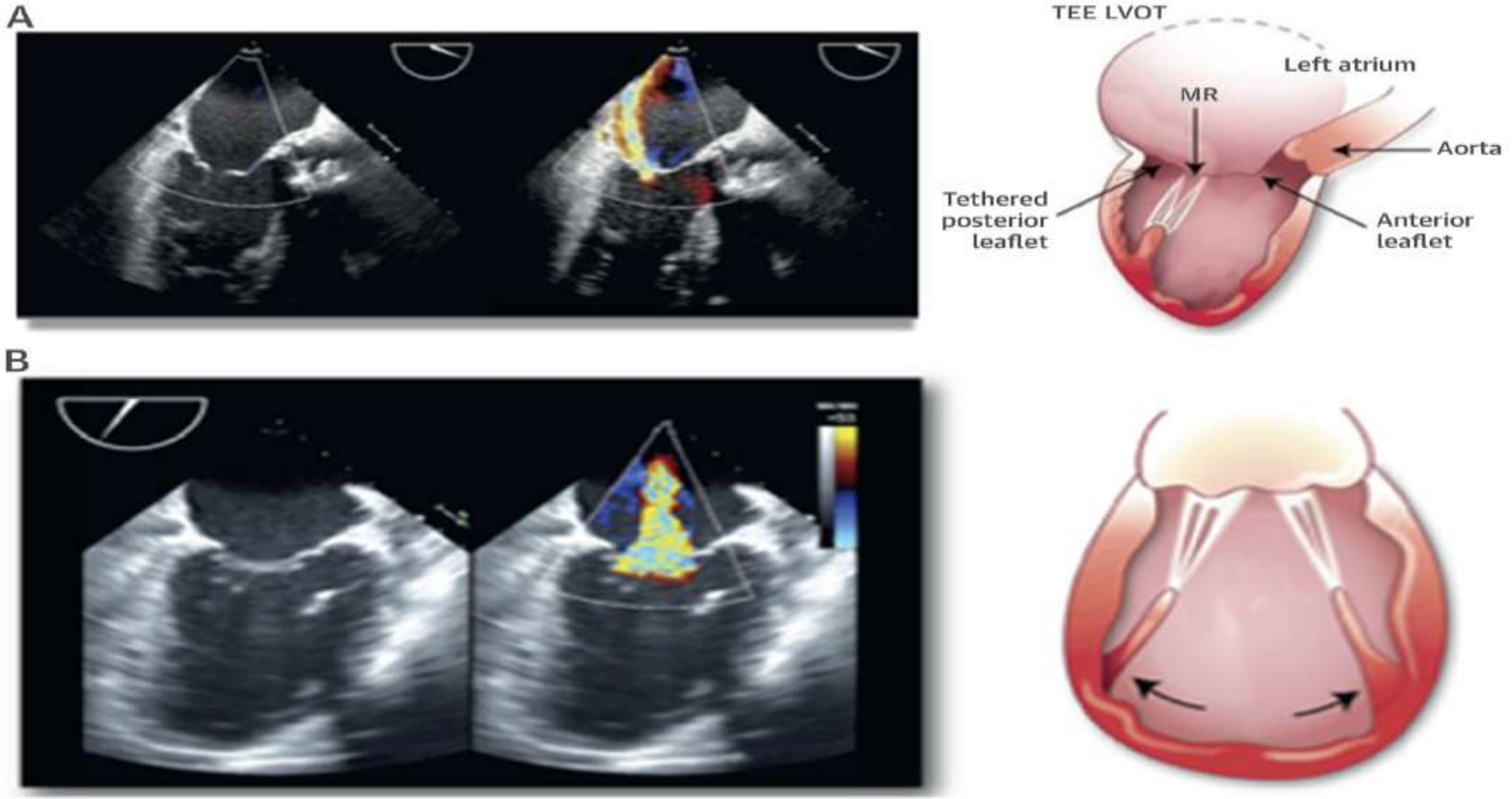
Ventricular Remodeling in Heart Failure

- Adverse ventricular remodeling is a common feature of advanced heart failure
- Progressive remodeling following myocardial injury is a result of neurohormonal activation
- Remodeling is characterized by left ventricular enlargement and transition from an elliptoid shape to a sphere



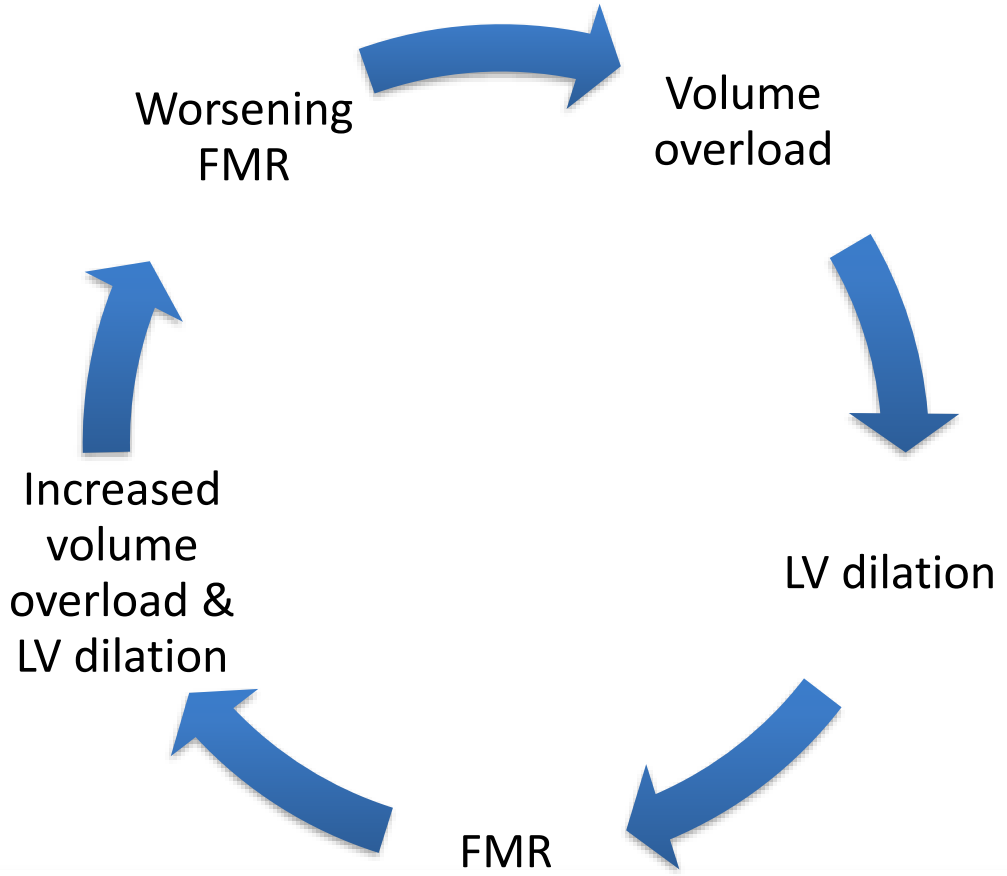
Jessup and Brozena, NEJM 2003

Etiology of Functional MR



Asgar et al. JACC 2015

The Vicious Cycle Of Heart Failure

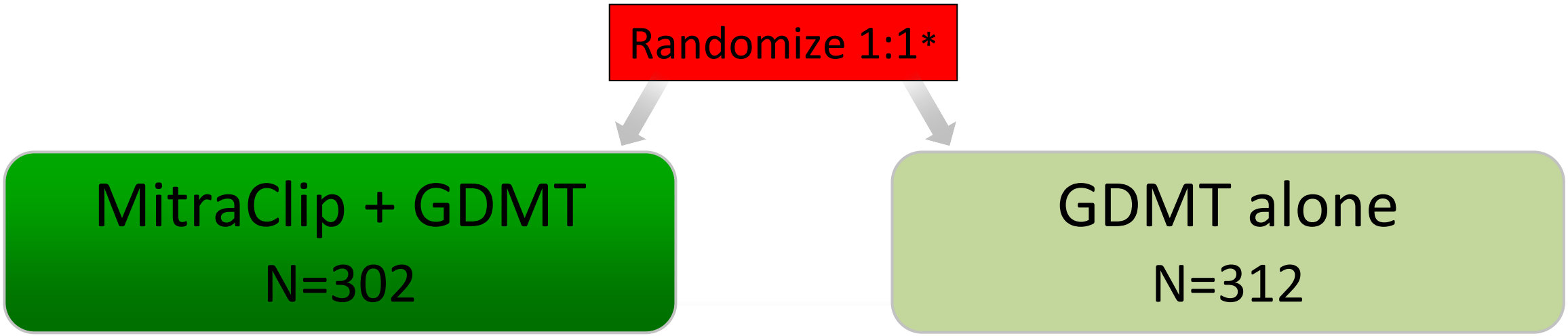


Can MitraClip interrupt this cycle or at least slow the progression?

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

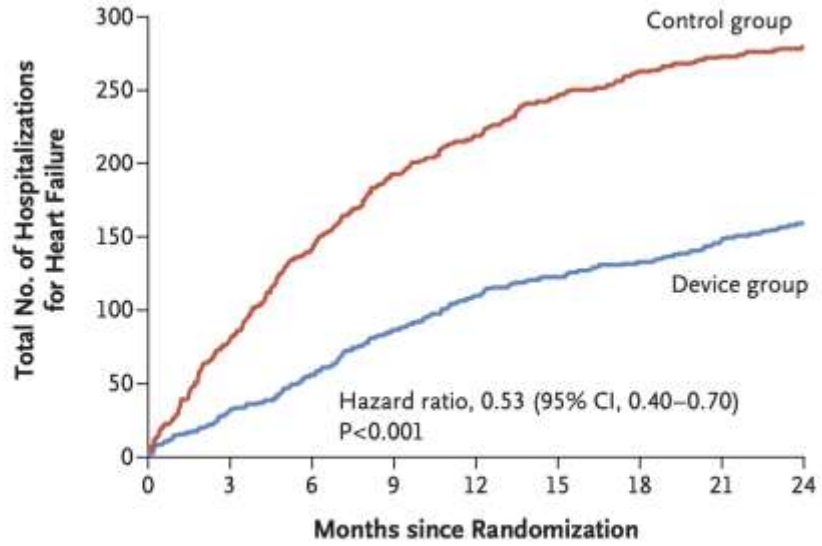
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Transcatheter Mitral-Valve Repair in Patients with Heart Failure

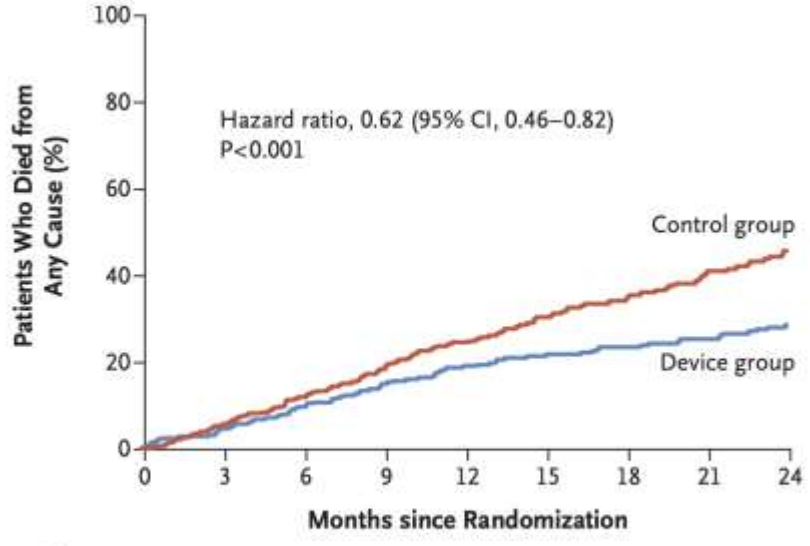
G.W. Stone, J.A. Lindenfeld, W.T. Abraham, S. Kar, D.S. Lim, J.M. Mishell, B. Whisenant, P.A. Grayburn, M. Rinaldi, S.R. Kapadia, V. Rajagopal,

A Hospitalization for Heart Failure



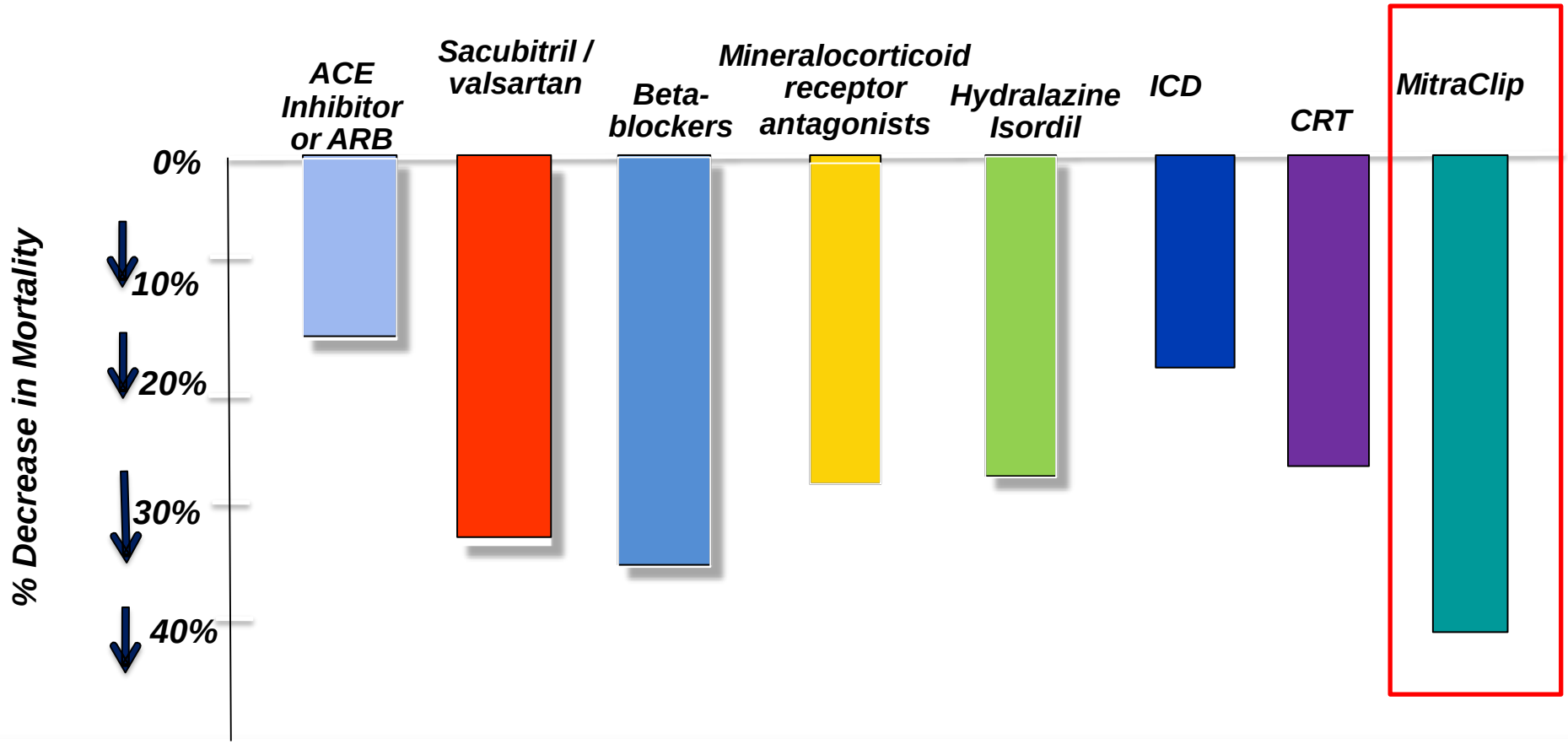
No. at Risk									
Control group	312	294	271	245	219	176	145	121	88
Device group	302	286	269	253	236	191	178	161	124

C Death from Any Cause



No. at Risk									
Control group	312	294	271	245	219	176	145	121	88
Device group	302	286	269	253	236	191	178	161	124

The Mortality Benefit of Therapies for HFrEF



RCTs of Transcatheter Mitral Valve Repair in Patients with Heart Failure

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*

The NEW ENGLAND JOURNAL of MEDICINE

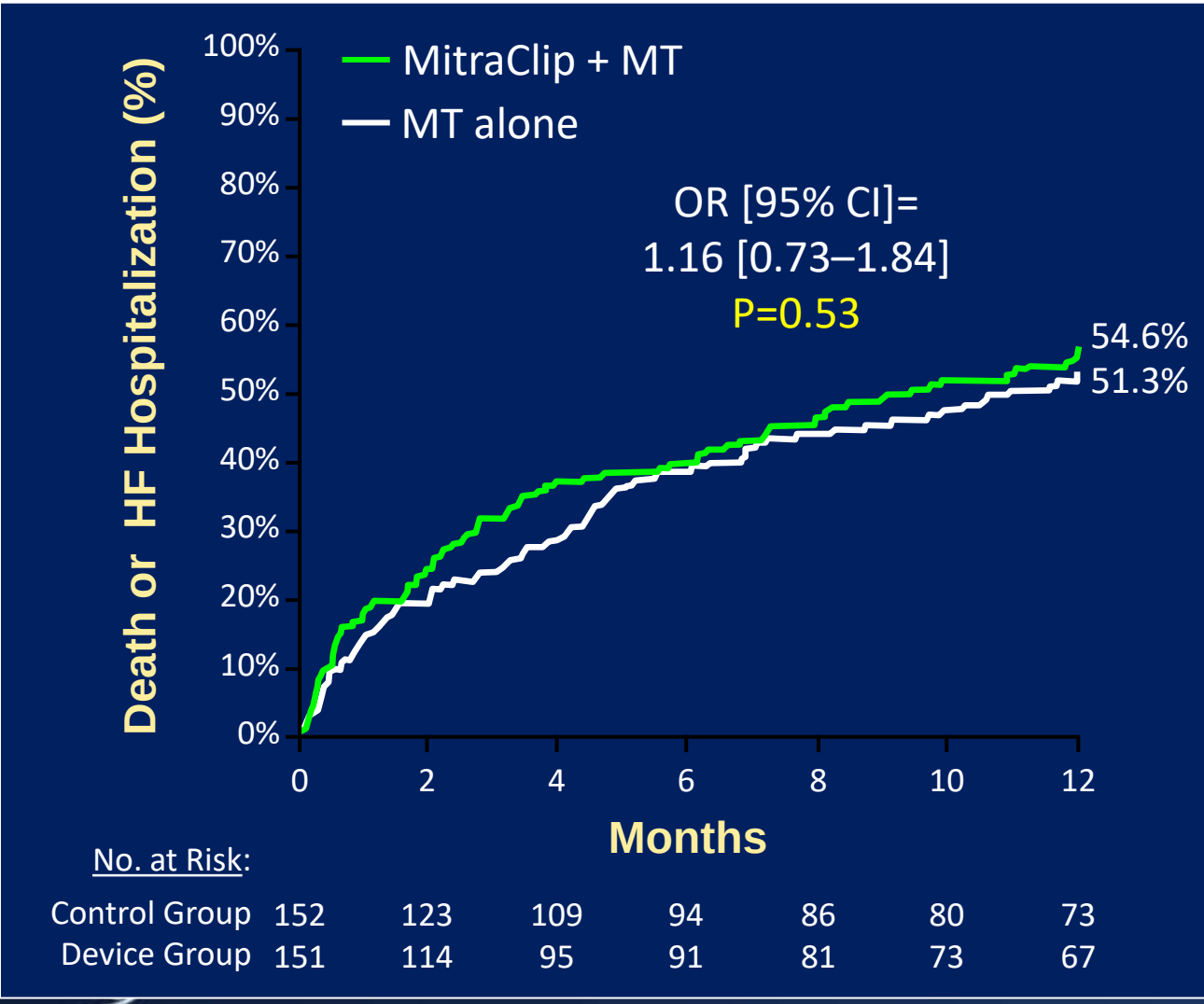
ORIGINAL ARTICLE

Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation

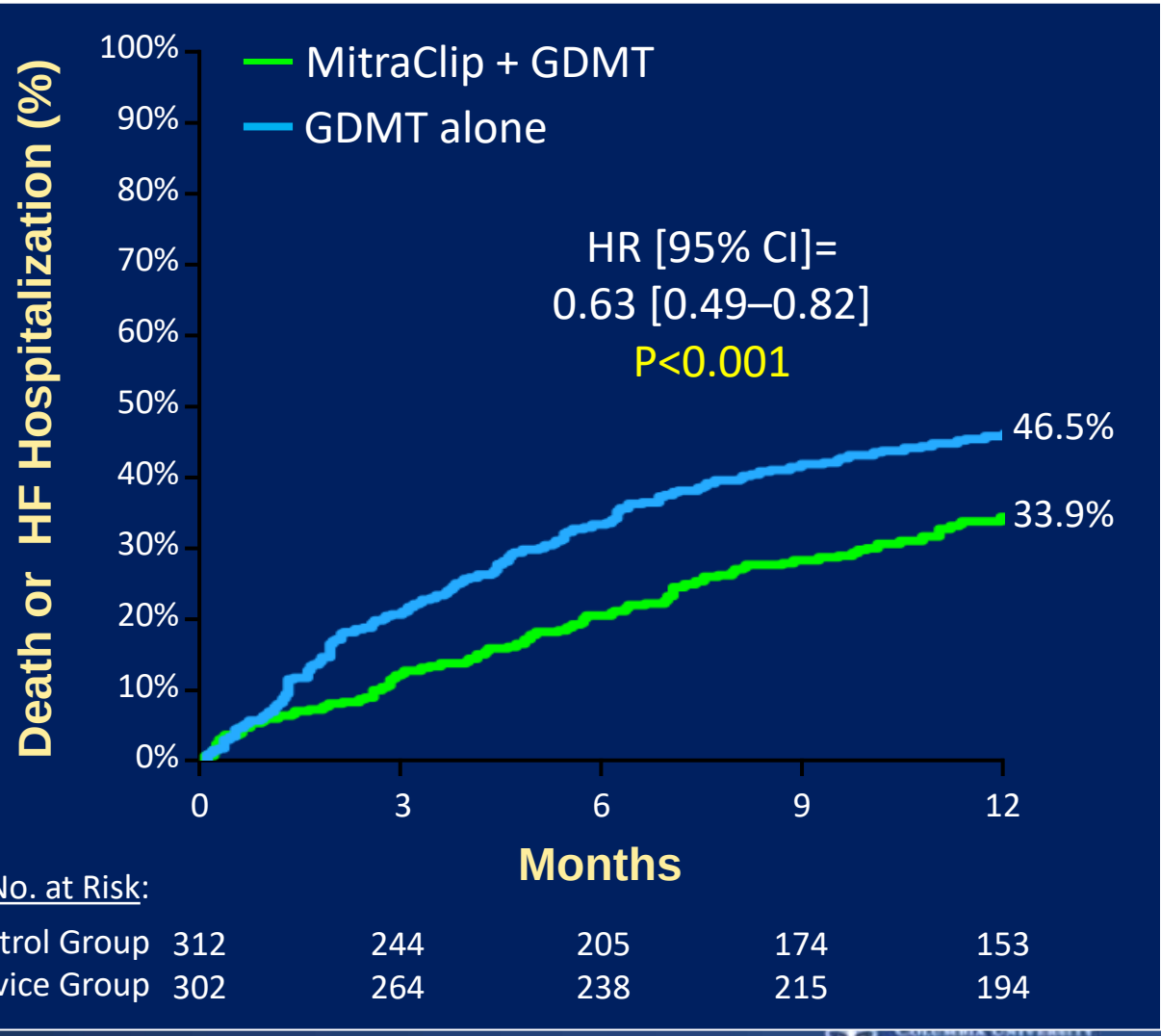
J.-F. Obadia, D. Messika-Zeitoun, G. Leurent, B. Iung, G. Bonnet, N. Piriou, T. Lefèvre, C. Piot, F. Rouleau, D. Carrié, M. Nejjari, P. Ohlmann, F. Leclercq, C. Saint Etienne, E. Teiger, L. Leroux, N. Karam, N. Michel, M. Gilard, E. Donal, J.-N. Trochu, B. Cormier, X. Armoiry, F. Boutitie, D. Maucort-Boulch,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

COAPT vs. MITRA-FR: 12-Month Death or HF Hosp

MITRA-FR



COAPT

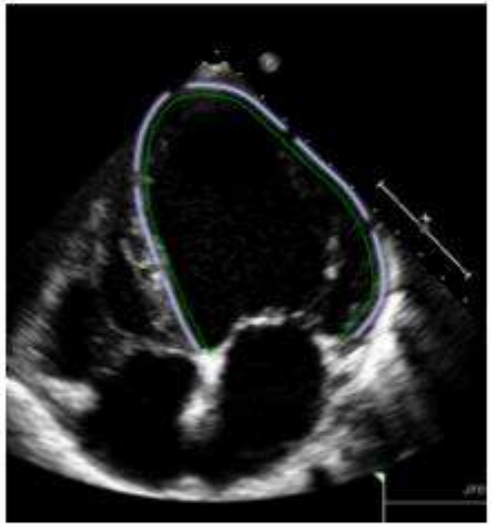


Why are the COAPT Results so Different from MITRA-FR?

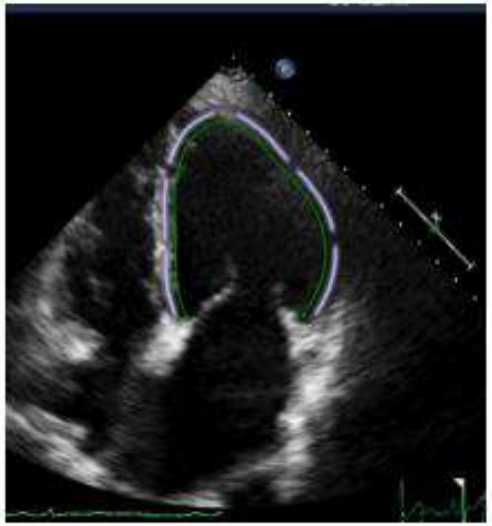
	MITRA-FR (n=304)	COAPT (n=614)
Severe MR entry criteria	Severe FMR by EU guidelines: EROA >20 mm^2 or RV >30 mL/beat	Severe FMR by US guidelines: EROA >30 mm^2 or RV >45 mL/beat
EROA (mean ± SD)	31 ± 10 mm^2	41 ± 15 mm^2
LVEDV (mean ± SD)	135 ± 35 mL/m^2	101 ± 34 mL/m^2

3 Patients with EROA of 30 mm2

LVEF 22%
LVEDV 310 mL
GLS -6.8%



LVEF 36%
LVEDV 197 mL
GLS -8.4%



LVEF 60%
LVEDV 140 mL
GLS -20.3%

LVAD, transplant, hospice

Spectrum of LV dysfunction

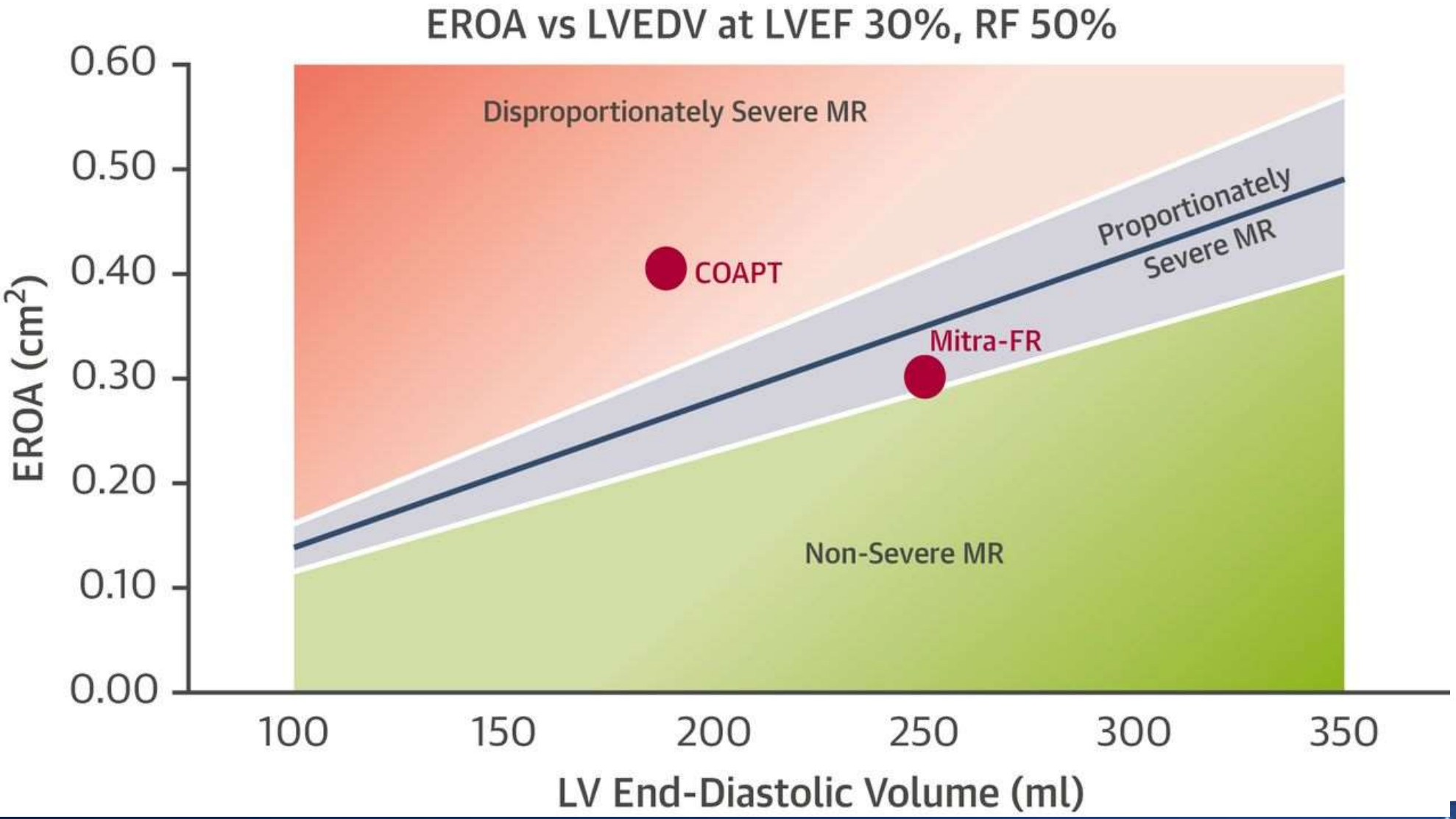
MR correction likely to be beneficial

LVEF, LV size, LV geometry
Severely abnormal

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

LVEF, LV size, LV geometry
Normal

Conceptual framework that distinguishes potential patients that may benefit from TMVr amongst the heterogeneous group of patients with FMR due to LV disease



Multiparametric Echo MR Assessment

Secondary MR, Severity 3+ or 4+ (Graded by 1 of 3 criteria

EROA ≥ 0.3 cm2
or
PV systolic flow reversal

N=570 (85.7%)

EROA 0.2 cm2 - <0.3 cm2
With any 1 of the following:
- RV ≥ 45 ml/beat
- RF ≥ 40%
- VC width ≥ 0.5 cm

N=70 (10.5%)

EROA <0.2 cm2 or NA
With at least 2 of the following:
- RV ≥ 45 ml/beat
- RF ≥ 40%
- VC width ≥ 0.5 cm
- PISA radius > 0.9 cm but no CW
- Large (≥ 6.0 cm) holosystolic jet wrapping around LA
- Peak E velocity ≥ 150 cm/s

N=25 (3.8%)

+ LVEF 20%-50% and LVESD ≤70 mm
No severe PHTN or RV failure

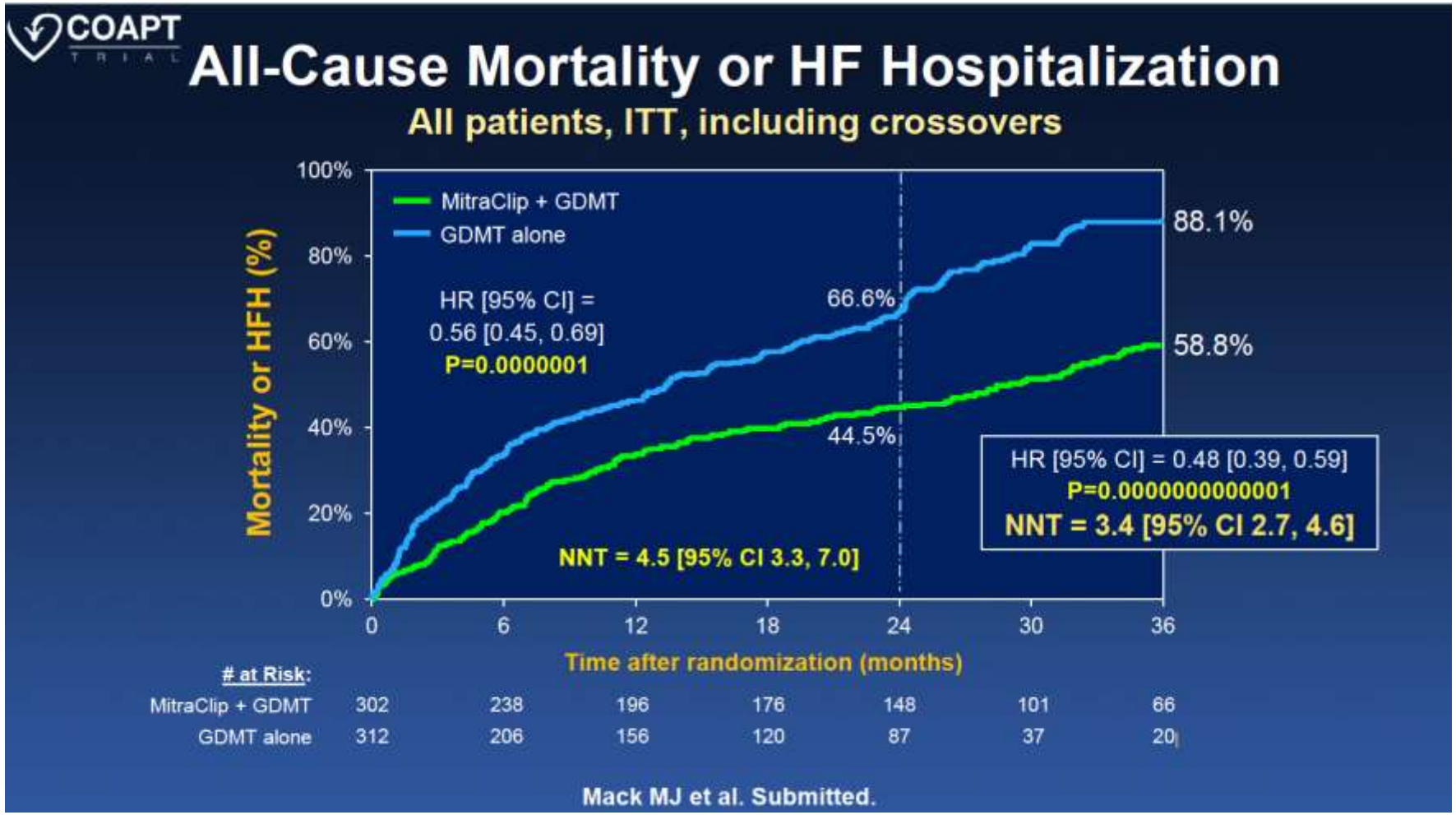
Why are the COAPT Results so Different from MITRA-FR?

	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

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

	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



Benefit sustained at longer term follow up

COAPT TRIAL

Primary Safety Endpoint (MitraClip arm)

Freedom from Device-related Complications

n=293 pts with MitraClip procedure attempted

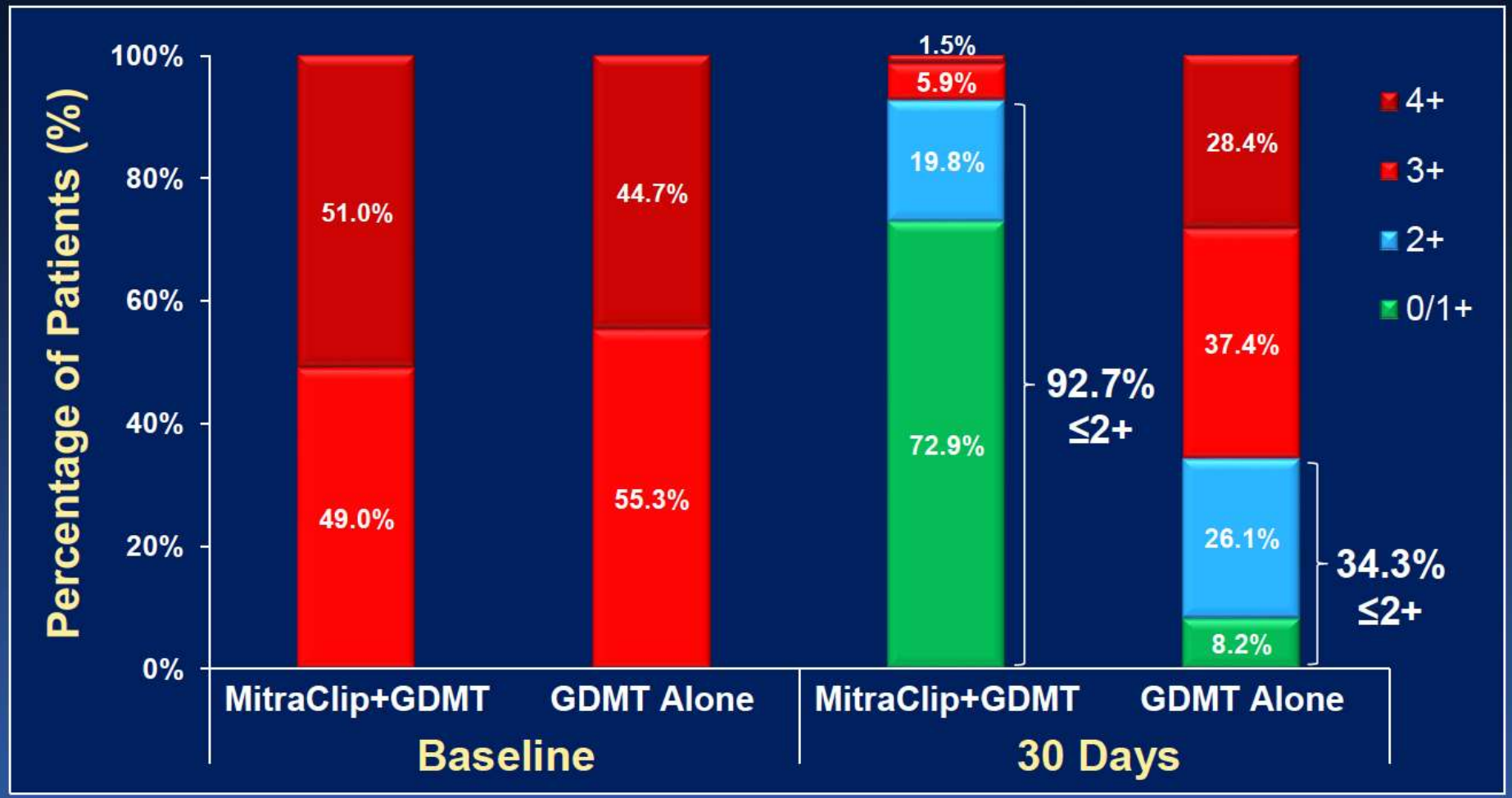
	0-30 Days	0-12 Months	0-24 Months	0-36 Months
All	**1.4% (4)**	**3.3% (9)**	**5.2% (13)**	**8.7% (18)**
- Device-related complications	**1.4% (4)**	**1.4% (4)**	**1.4% (4)**	**1.4% (4)**
• Single leaflet device attachment	0.7% (2)	0.7% (2)	0.7% (2)	0.7% (2)
• Device embolization	0.3% (1)	0.3% (1)	0.3% (1)	0.3% (1)
• Endocarditis requiring surgery	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
• Mitral stenosis requiring surgery	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
• Any device-related complication requiring non-elective CV surgery	0.3% (1)	0.3% (1)	0.3% (1)	0.3% (1)
- Progressive heart failure	**0.0% (0)**	**2.0% (5)**	**3.8% (9)**	**7.4% (14)**
• Left ventricular assist device implant	0.0% (0)	1.2% (3)	2.6% (6)	5.4% (10)
• Heart transplant	0.0% (0)	0.8% (2)	1.3% (3)	2.6% (5)

Mack MJ et al. Submitted.

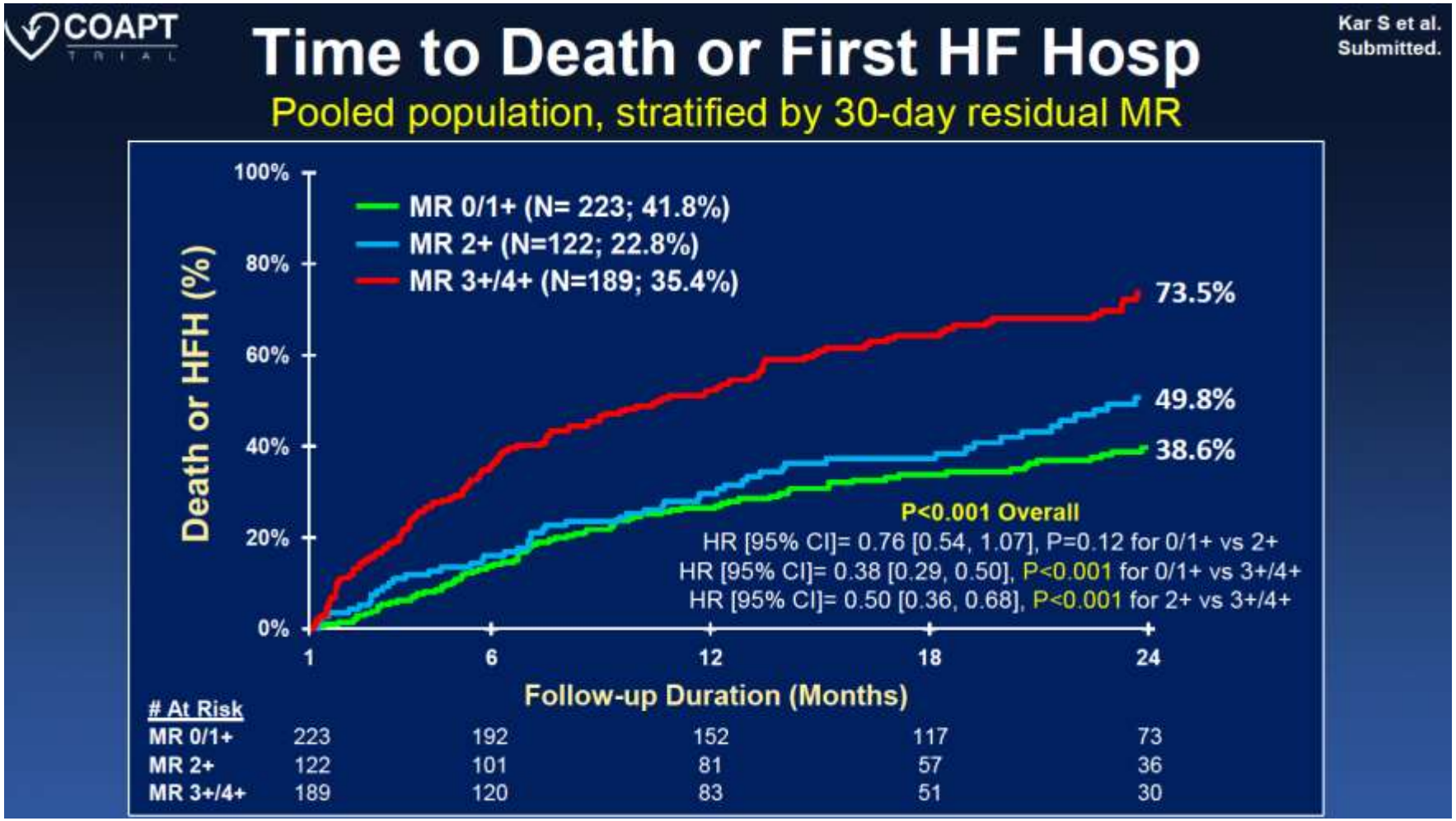
Primary safety endpoint

COAPT TRIAL

MR Reduction in COAPT

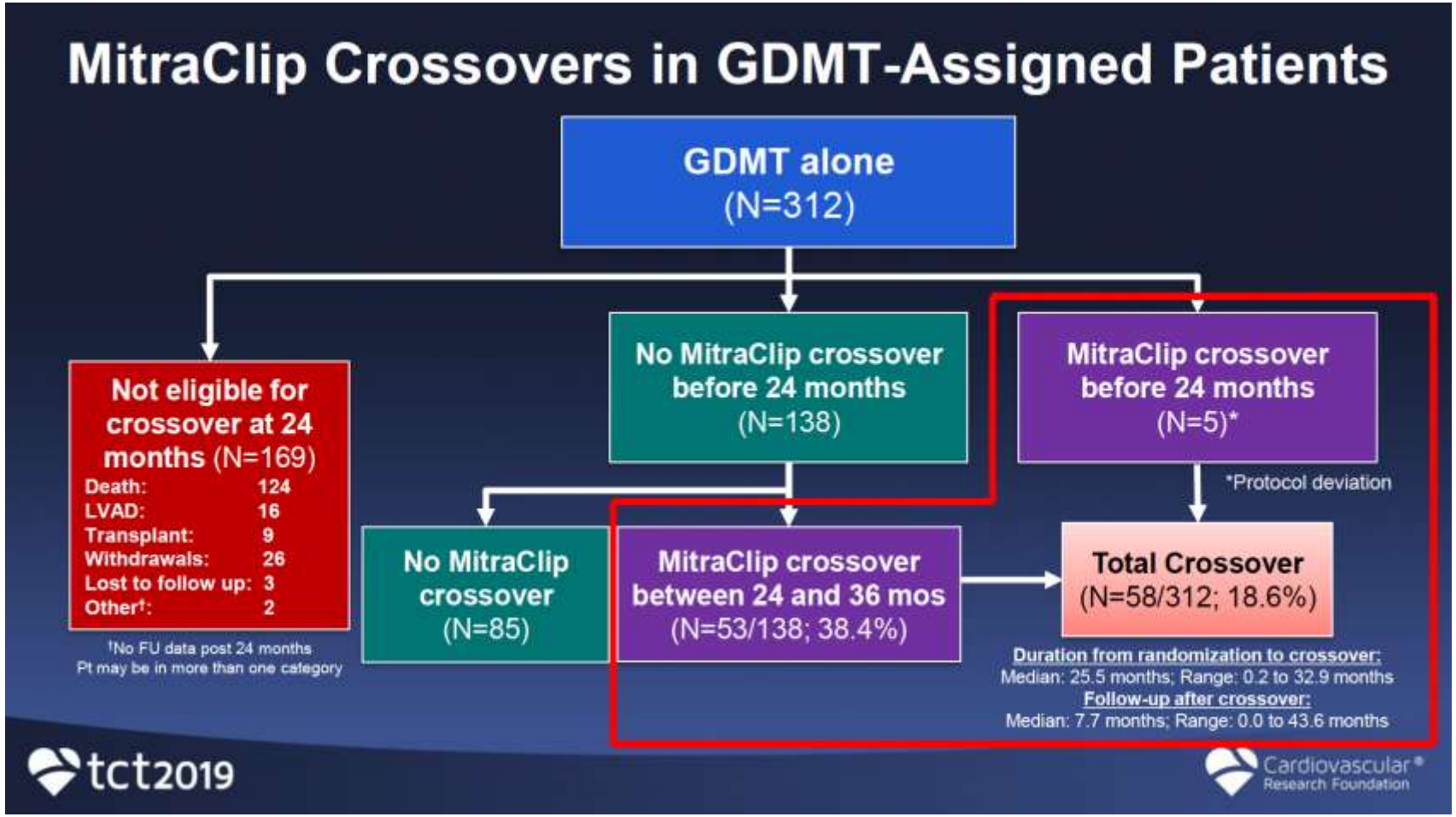


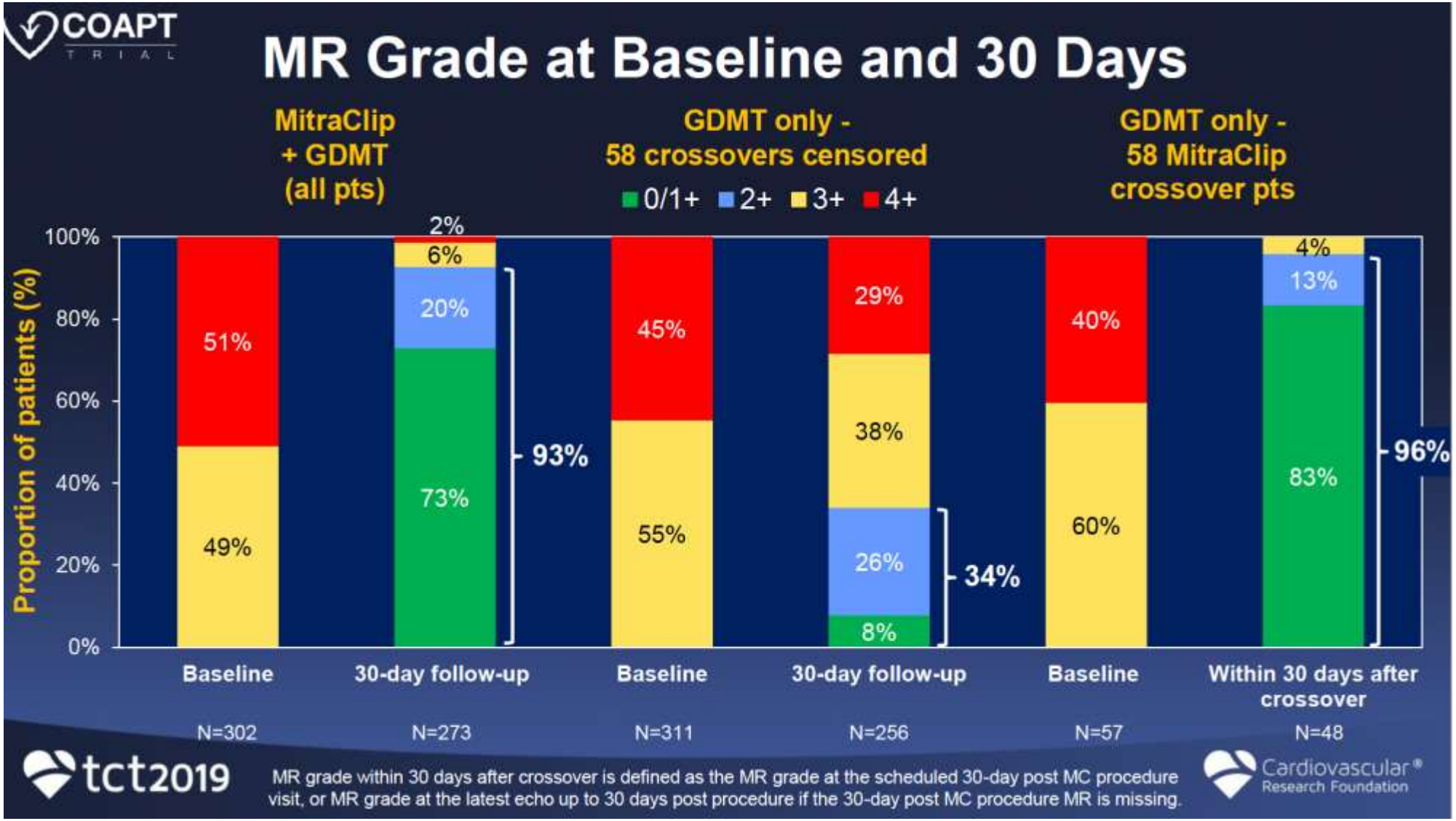
Stone GW et al. N Engl J Med. 2018;379:2307-18



Outcomes determined by procedural result

What do the crossovers show us?




COAPT TRIAL
MR Grade at Baseline and 30 Days
MitraClip + GDMT (all pts)
GDMT only - 58 crossovers censored
GDMT only - 58 MitraClip crossover pts
0/1+
2+
3+
4+
Proportion of patients (%)
100%
80%
60%
40%
20%
0%
51%
49%
2%
6%
20%
73%
93%
45%
55%
29%
38%
26%
8%
34%
40%
60%
4%
13%
83%
96%
Baseline
30-day follow-up
Baseline
30-day follow-up
Baseline
Within 30 days after crossover
N=302
N=273
N=311
N=256
N=57
N=48
tct2019
MR grade within 30 days after crossover is defined as the MR grade at the scheduled 30-day post MC procedure visit, or MR grade at the latest echo up to 30 days post procedure if the 30-day post MC procedure MR is missing.
Cardiovascular Research Foundation

Treatment with MitraClip, even late, provides clinical benefit

COAPT TRIAL

All-Cause Mortality or HF Hospitalization

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

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

tct2019

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

Cardiovascular Research Foundation

Multivariable Predictors of Death or HFH Within 36 Months

GDMT only group with MitraClip crossover as a time-adjusted covariate

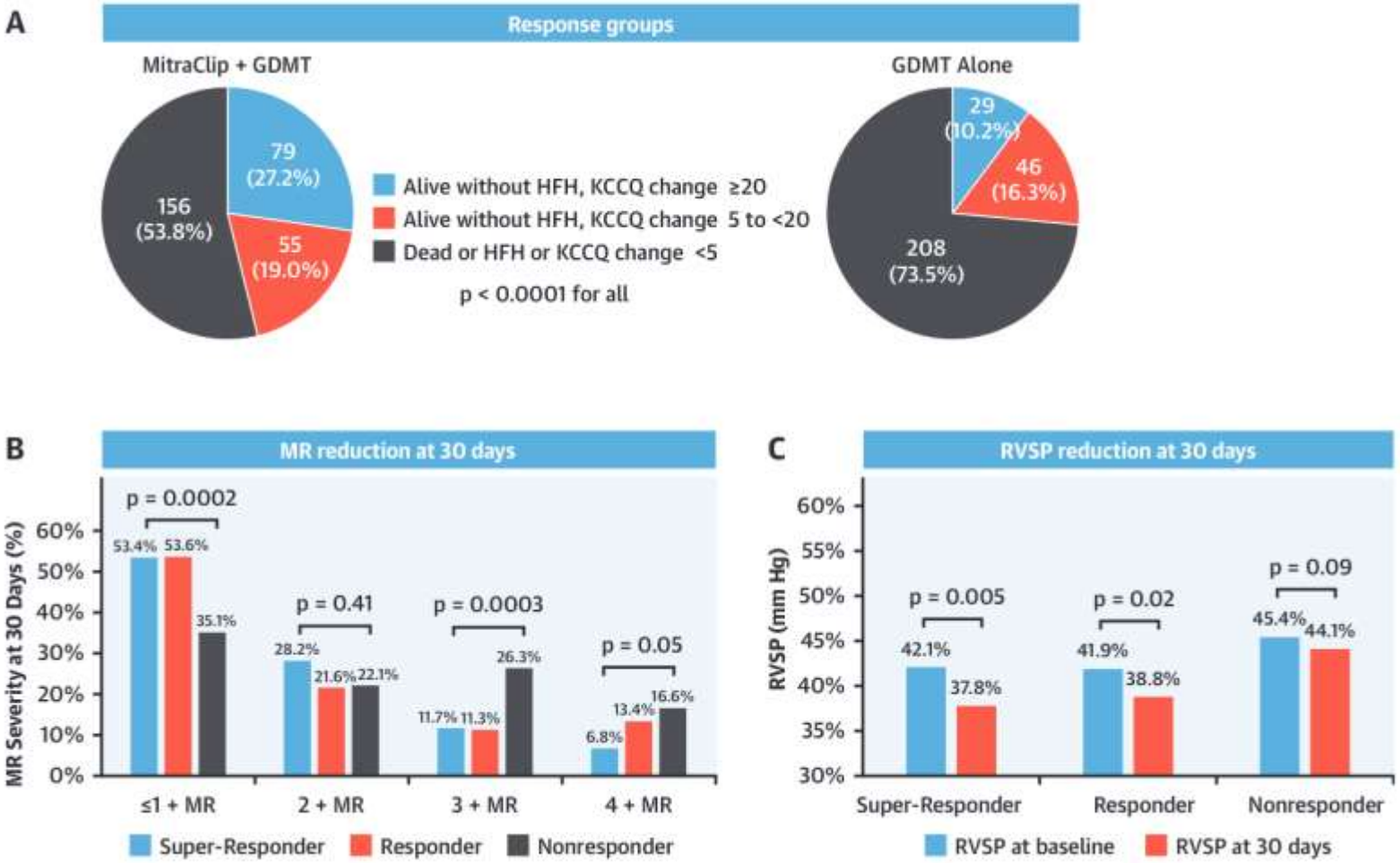
	Hazard Ratio [95% CI]	P-Value
Treatment with MitraClip	0.43 [0.24, 0.78]	0.006
BNP (per 100 pg/mL)	1.02 [1.01, 1.03]	<0.0001
Vasodilator use (hydralazine or nitrates)	1.91 [1.37, 2.66]	0.0001
Systolic blood pressure (per 1 mmHg)	0.99 [0.98, 1.00]	0.004
STS replacement score (per 1 unit)	1.04 [1.01, 1.07]	0.005
Beta-blocker use	0.57 [0.37, 0.88]	0.01
LVEDV (per 10 mL)	1.02 [1.00, 1.04]	0.02

Variables entered the final model include: ACEi/ARB/ARNI use, aldosterone inhibitor use, history of anemia, beta-blocker use, BNP, serum creatinine, treatment with MitraClip, EROA, sex, vasodilators (hydralazine or nitrates), LVEDV, LVEF, prior PCI/CABG, renal disease, 6MWD, prior stroke, STS replacement score, SBP, TR grade; other variables tested had α>0.20 in univariable analysis, were colinear with the present variables or had <90% values

tct2019

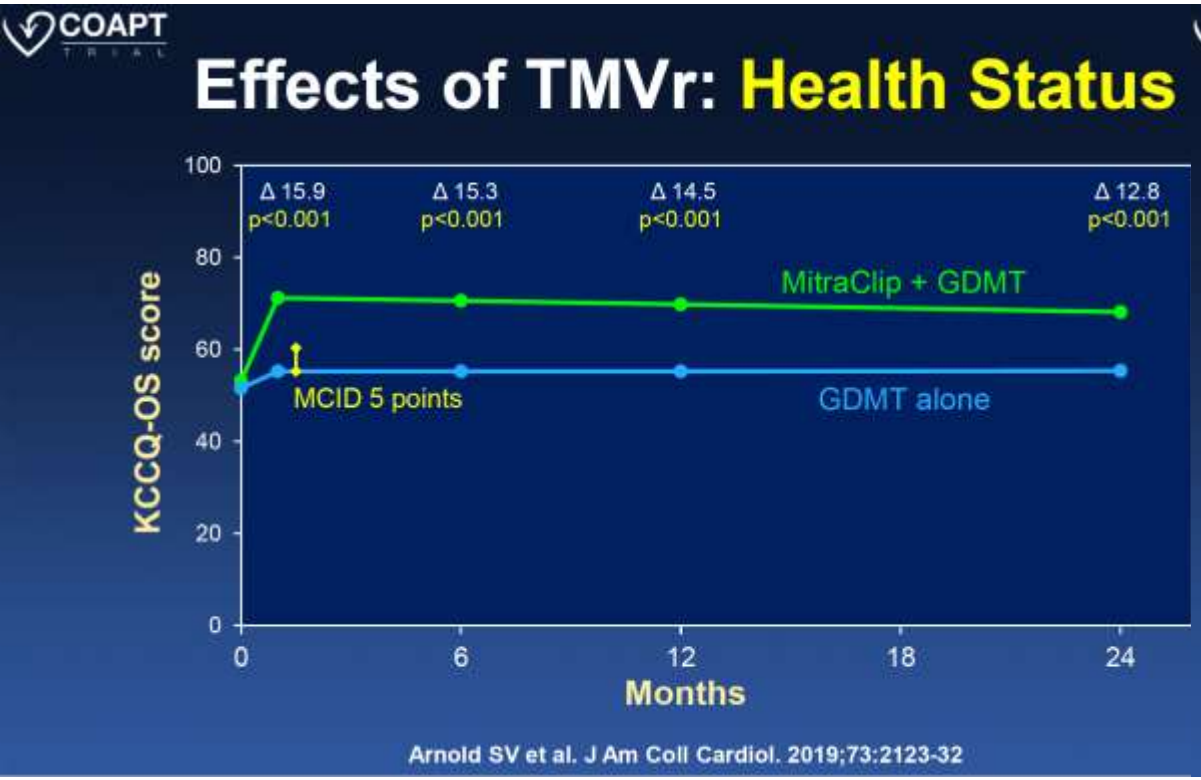
Cardiovascular Research Foundation

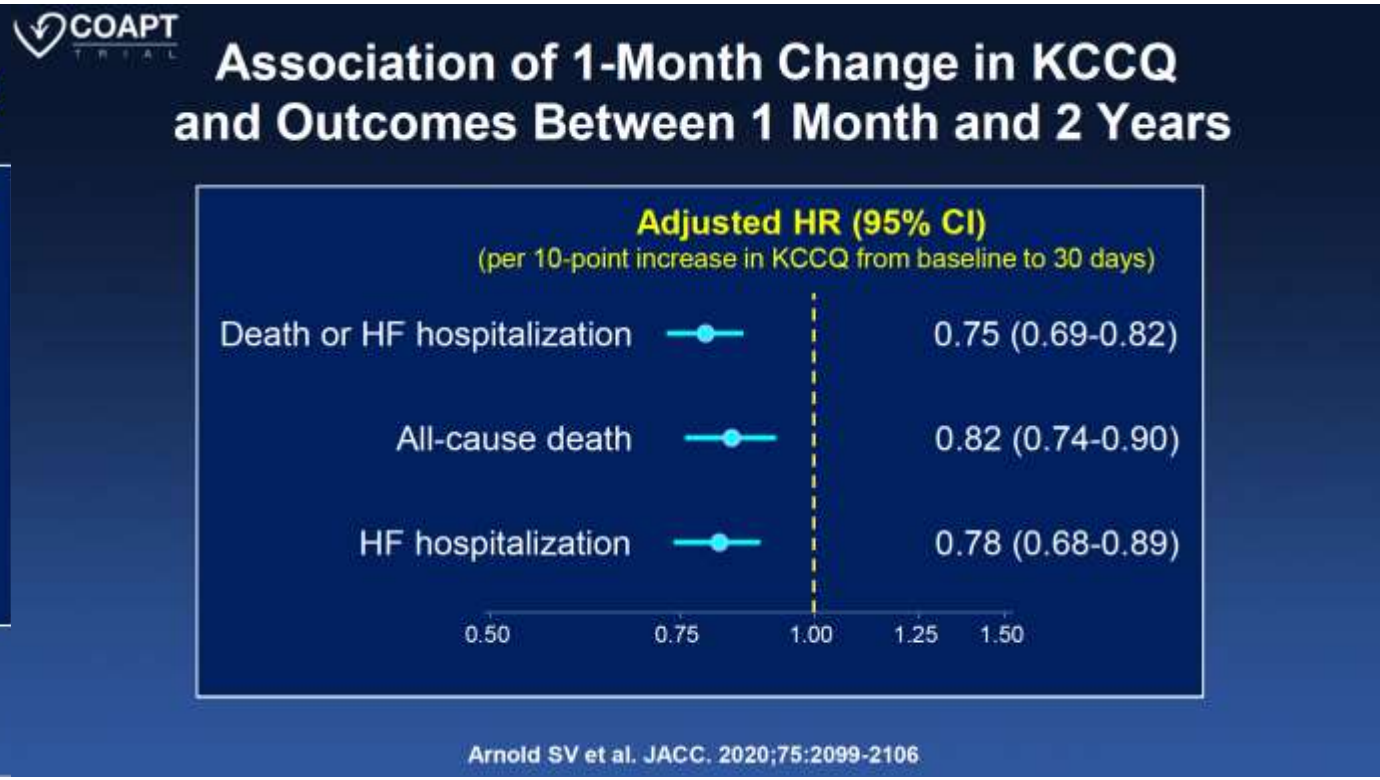
Responders vs Non-Responders



Grayburn, P.A. et al. J Am Coll Cardiol. 2020;76(9):1007-14.

Early clinical benefit results in improved long term outcomes

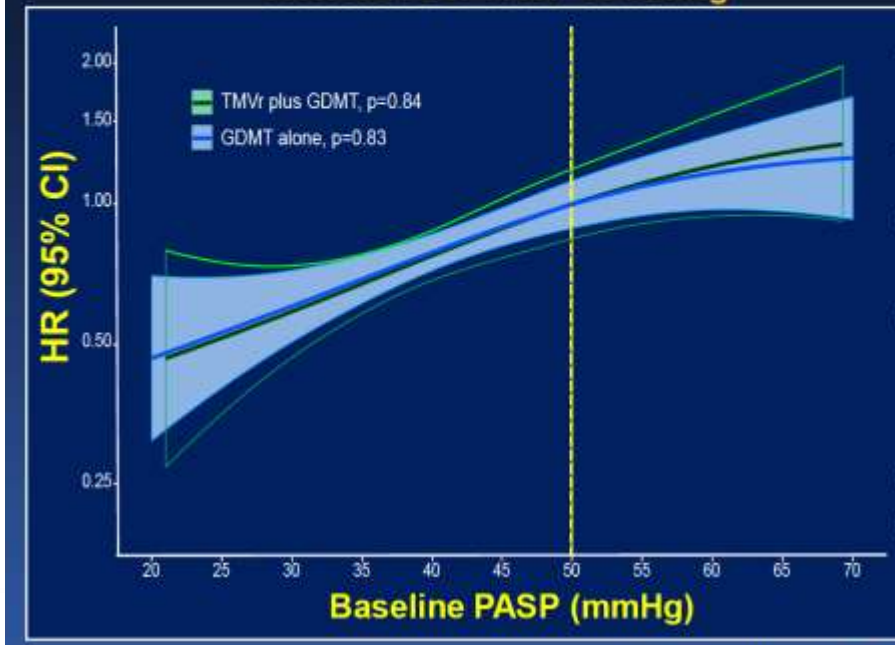




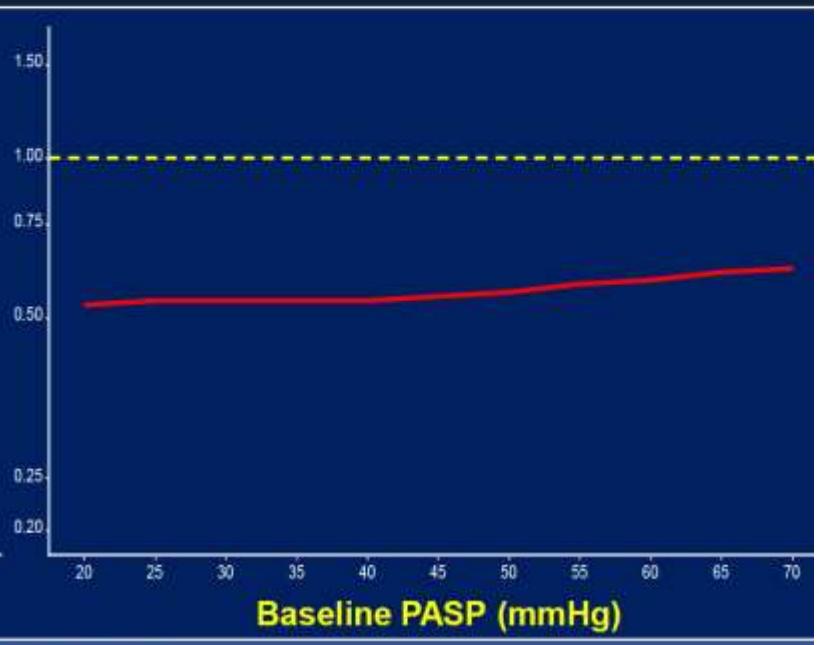
Impact of Pulmonary HTN

2-year Death or HFH after MitraClip vs. GDMT alone

HR for MitraClip and GDMT alone separately, referenced to PASP 50 mmHg

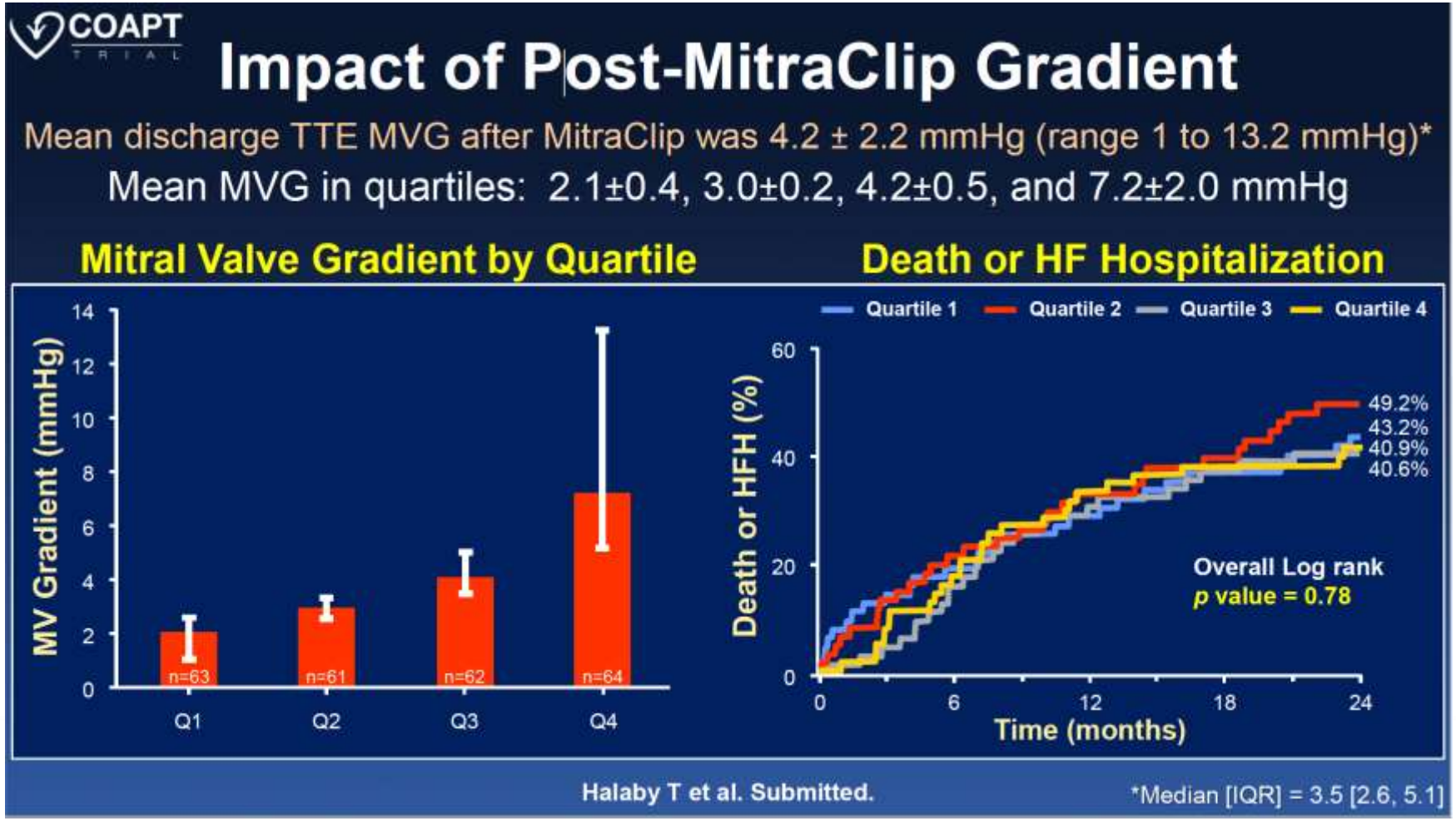


HR for MitraClip vs. GDMT alone



Ben-Yehuda O et al. Submitted.

Impact of Mitral Gradient on Outcomes



MitraClip in Heart Failure – What have we learned?

- Treatment with MitraClip in patients with heart failure despite GDMT results in sustained clinical benefit
- Late treatment provides the same clinical benefit
- Clinical outcomes linked to quality of life benefit
- Patients with pulmonary hypertension or residual gradient also derive the benefit
- Future studies will need to determine whether indications should be broadened (anatomic restrictions, earlier treatment, etc.)

Ideal Candidate for MitraClip in Heart Failure

- Favorable anatomy (lack of calcium, clefts, broad jets, small MVA)
- P
- Sy
- E