

Treatment of Mitral Regurgitation in Heart Failure

New Insights from COAPT

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and the Cardiovascular Research Foundation

Disclosure Statement

Gregg W. Stone MD

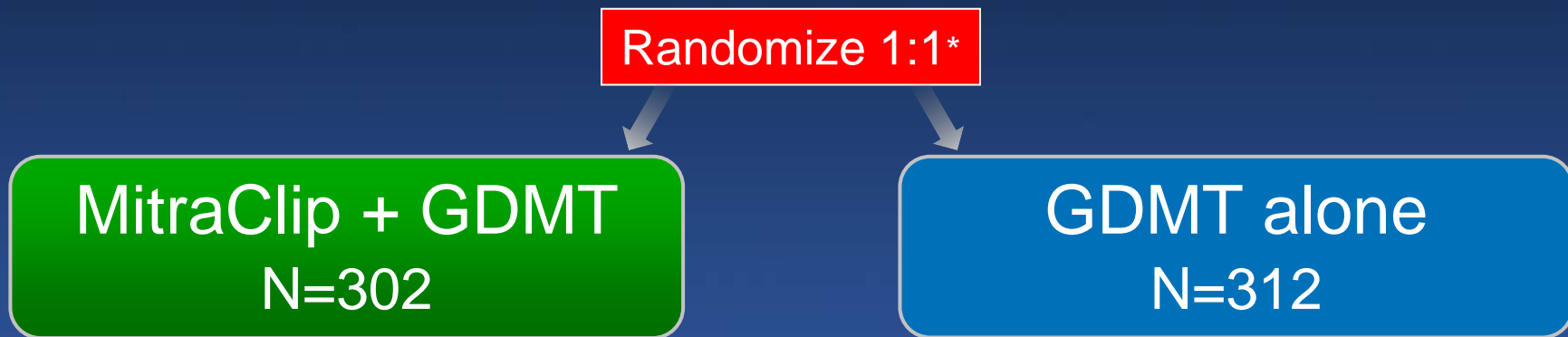
Consulting fees from Neovasc, Valfix, Ancora, Cardiomech
Equity/options from Ancora, Valfix, Cardiac Success

Principal investigator for the COAPT trial - UNPAID

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



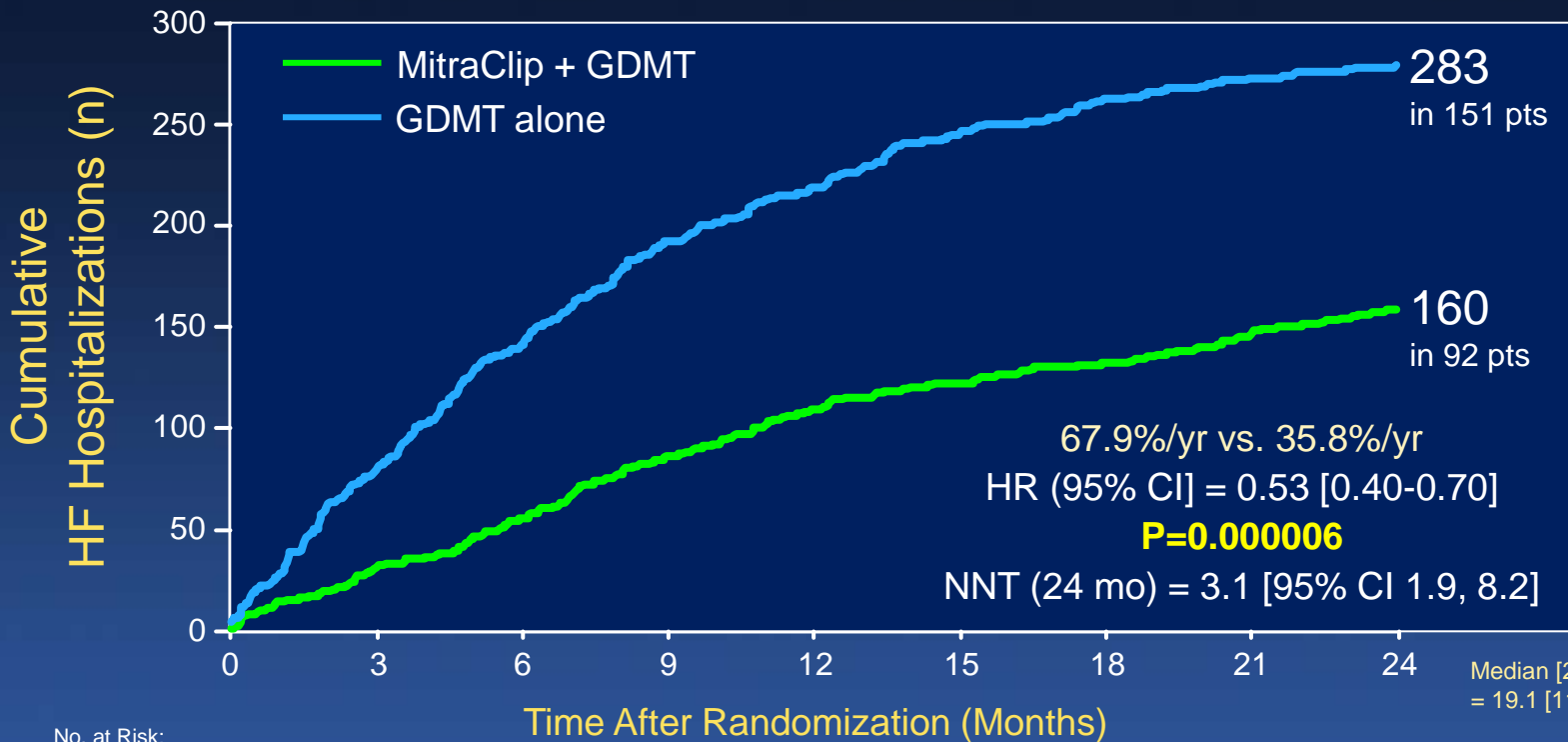
*Stratified by cardiomyopathy etiology (ischemic vs. non-ischemic) and site

Key Entry Criteria

1. Ischemic or non-ischemic cardiomyopathy with **LVEF 20%-50%** and **LVESD \leq 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. Exclusions: PASP $>$ 70 mmHg not responsive to vasodilators; mod/sev RV dysfunction; TR requiring surgery

Primary Effectiveness Endpoint

All Hospitalizations for HF within 24 months

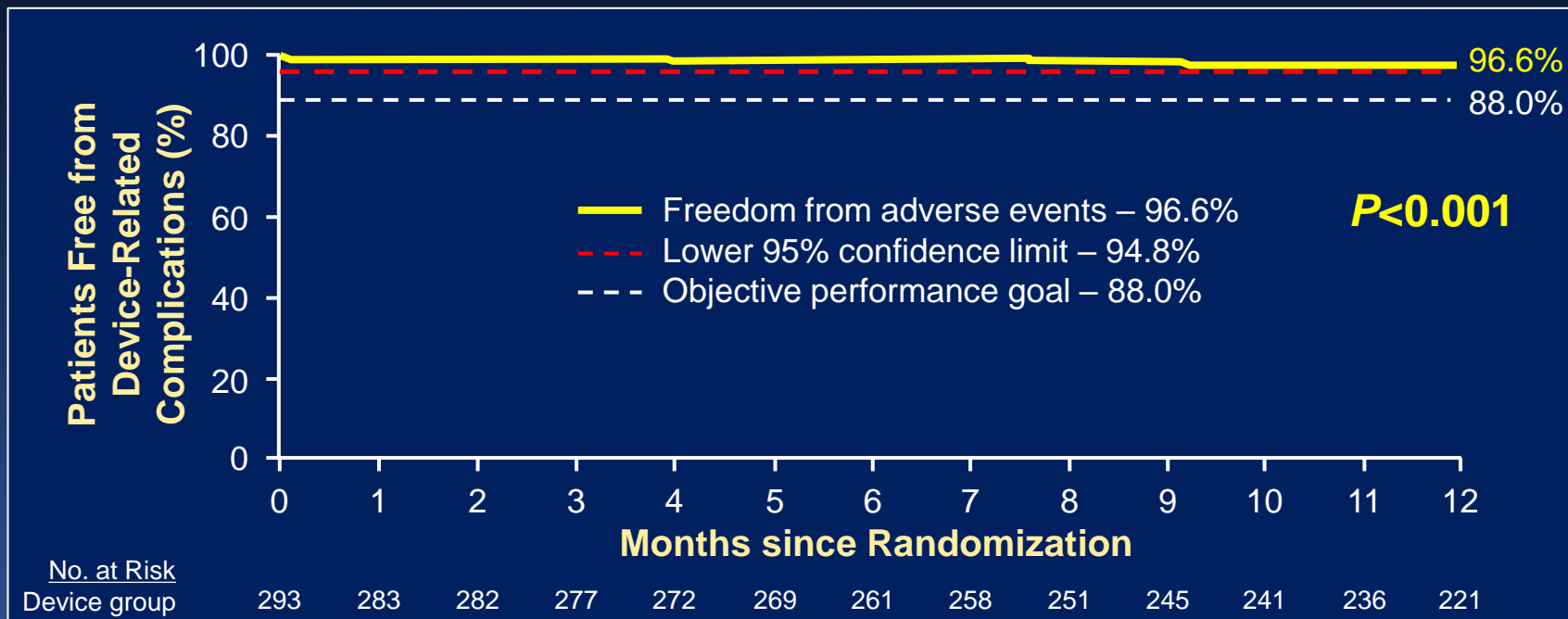


No. at Risk:

	0	3	6	9	12	15	18	21	24
MitraClip	302	286	269	253	236	191	178	161	124
GDMT	312	294	271	245	219	176	145	121	88

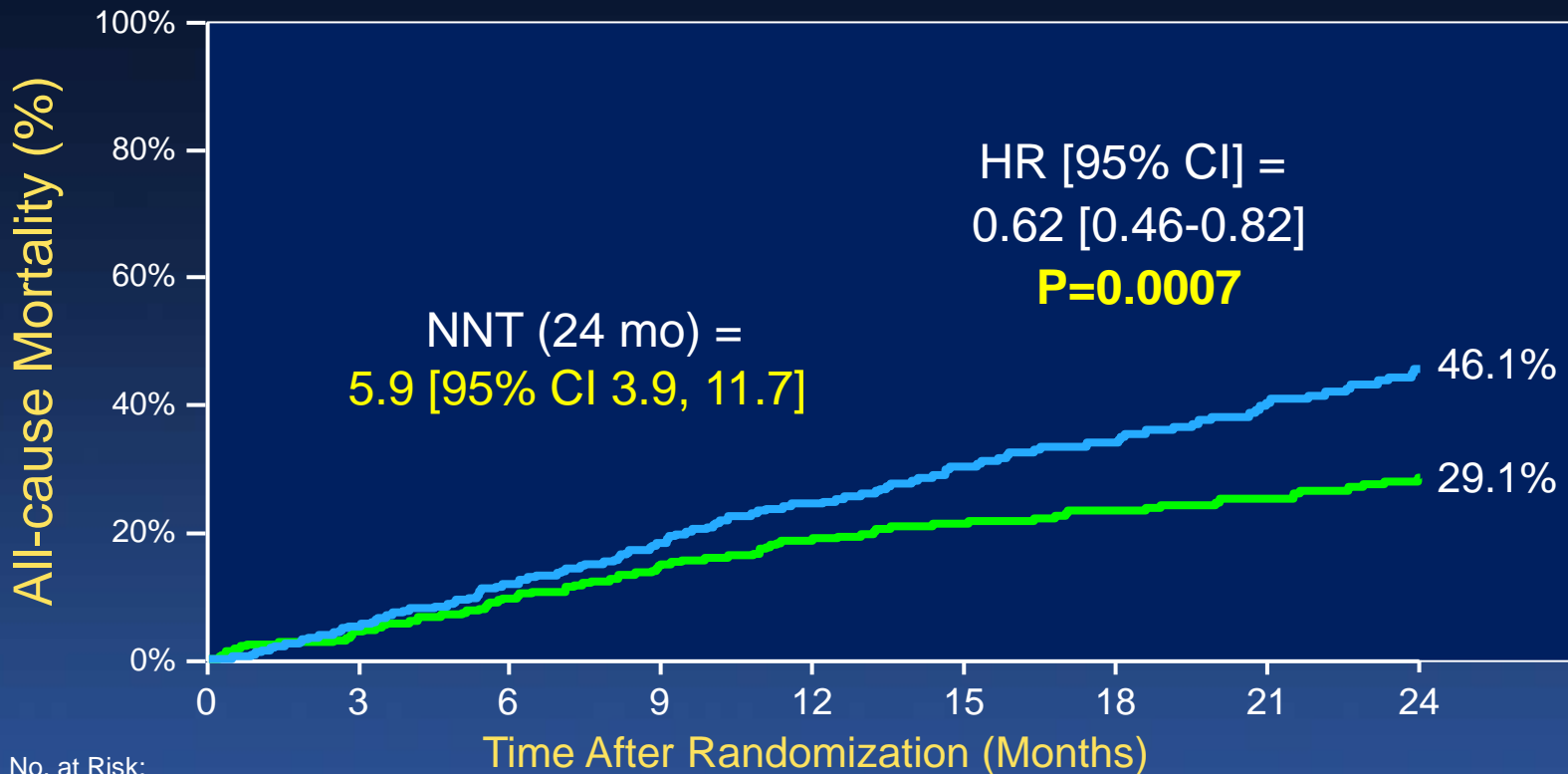
Primary Safety Endpoint

Freedom from device-related complications* within 12 months



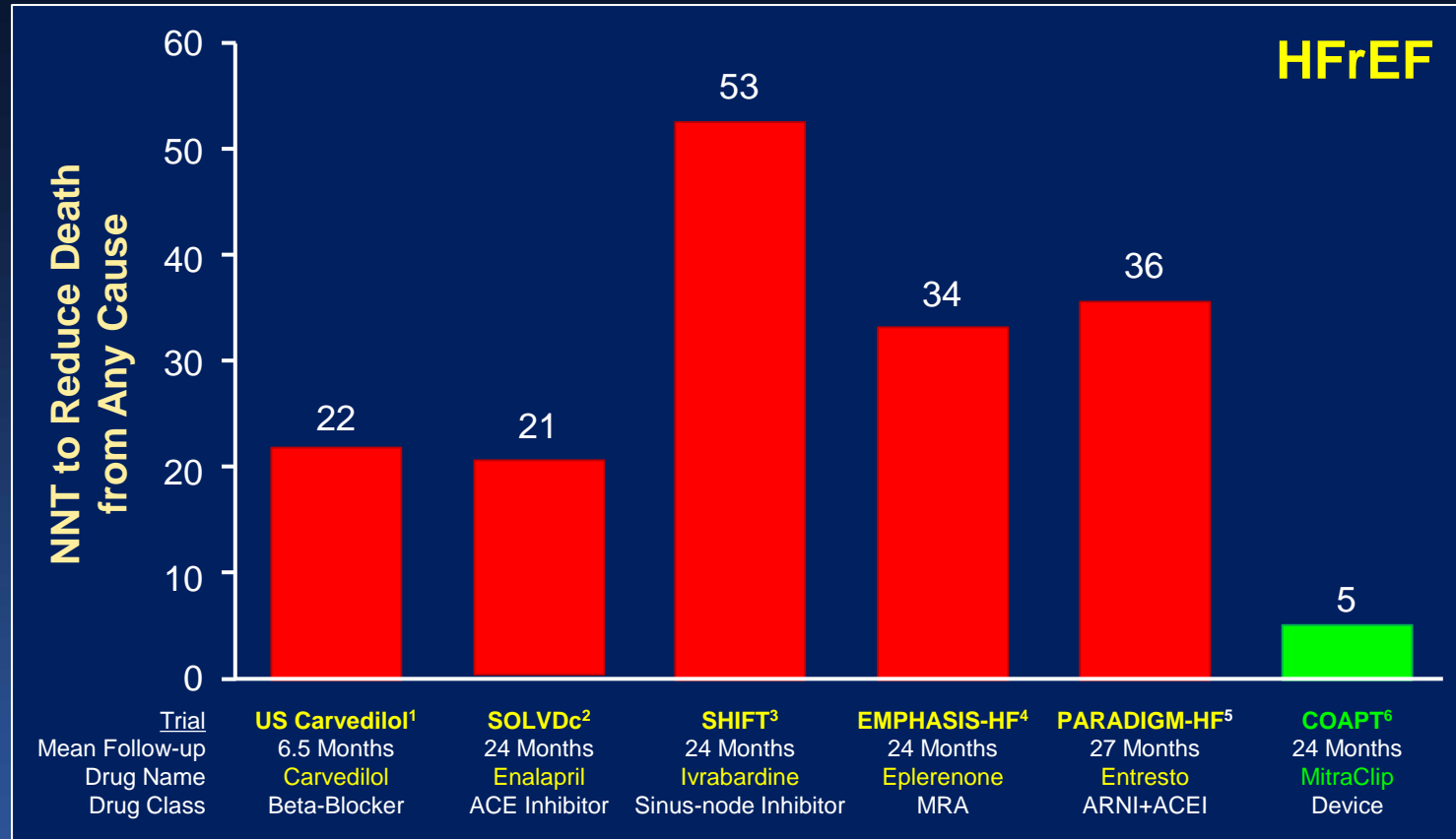
* SLDA, device embolization, endocarditis or MS requiring surgery, LVAD, OHT, any device-related compl requiring non-elective CV surgery. P value calculated from Z test with Greenwood's method of estimated variance against a pre-specified OPG of 88%

All-cause Mortality



No. at Risk:	0	3	6	9	12	15	18	21	24
MitraClip + GDMT	302	286	269	253	236	191	178	161	124
GDMT alone	312	294	271	245	219	176	145	121	88

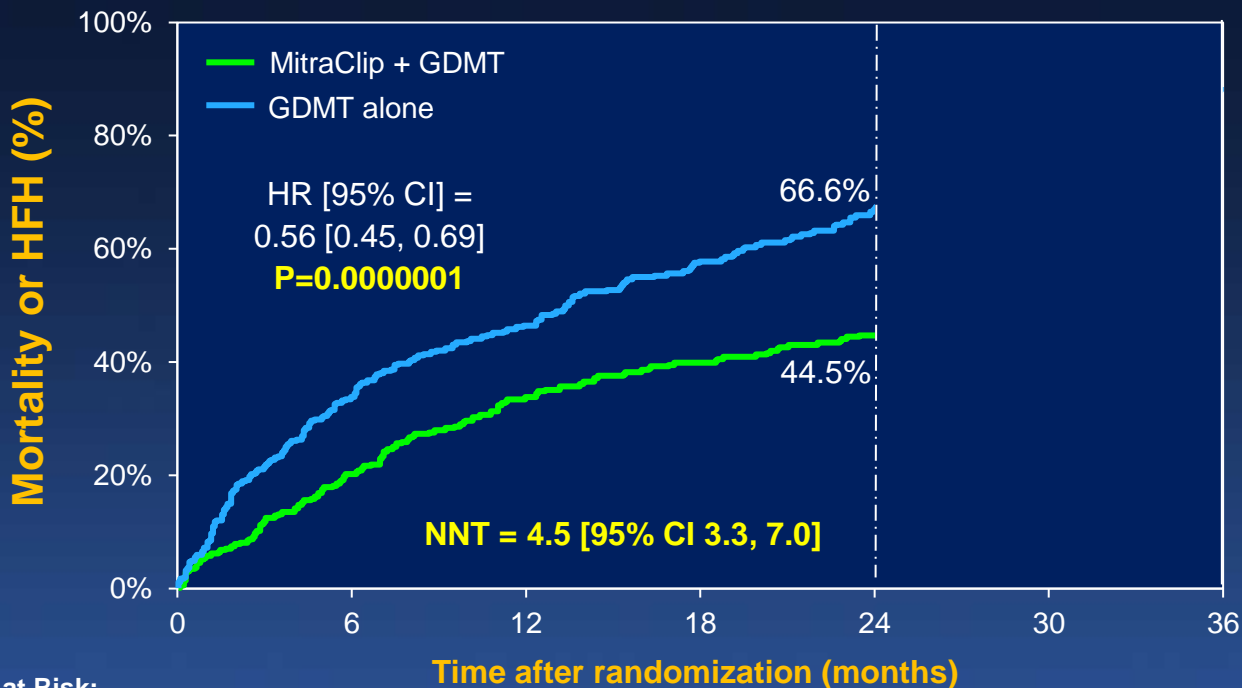
Number Needed to Treat (NNT) to Prevent 1 Death



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.

All-Cause Mortality or HF Hospitalization

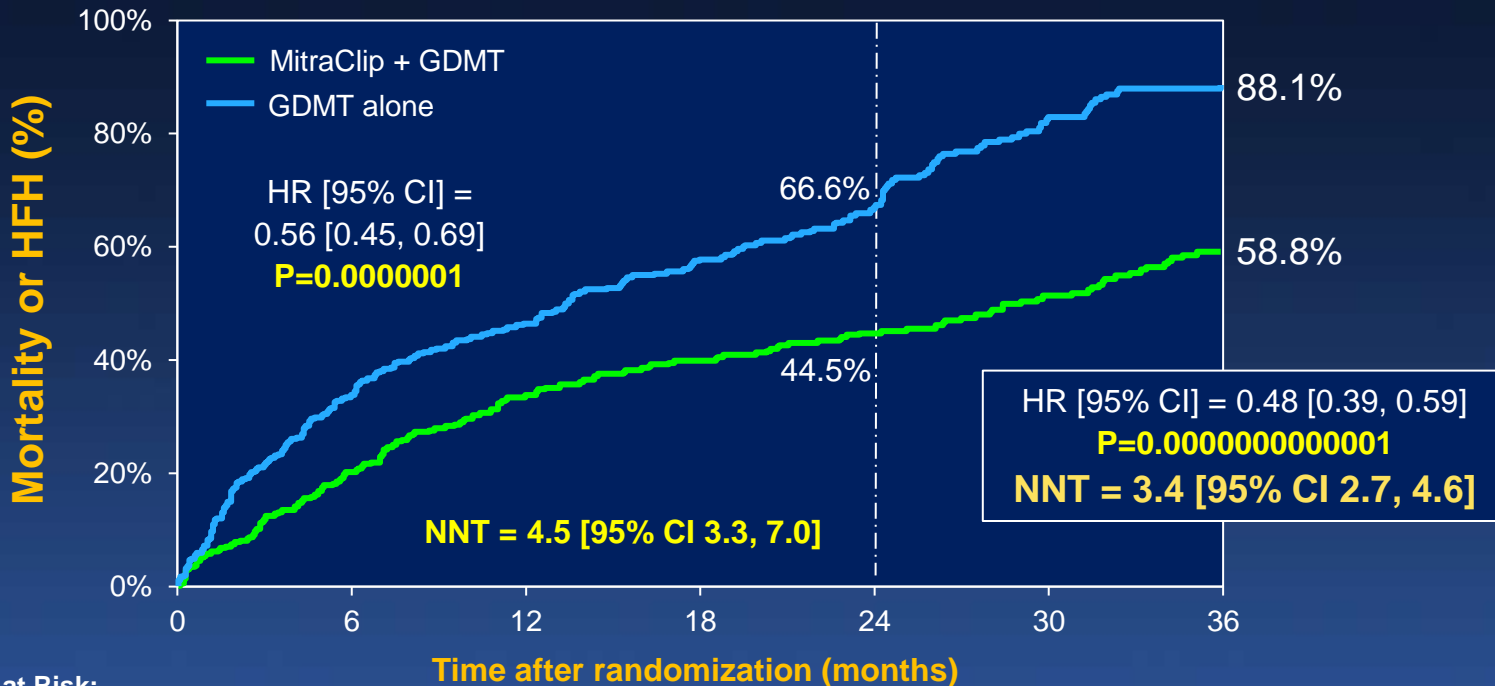
All patients, ITT, including crossovers



	# at Risk:				
	0	6	12	18	24
MitraClip + GDMT	302	238	196	176	148
GDMT alone	312	206	156	120	87

All-Cause Mortality or HF Hospitalization

All patients, ITT, including crossovers

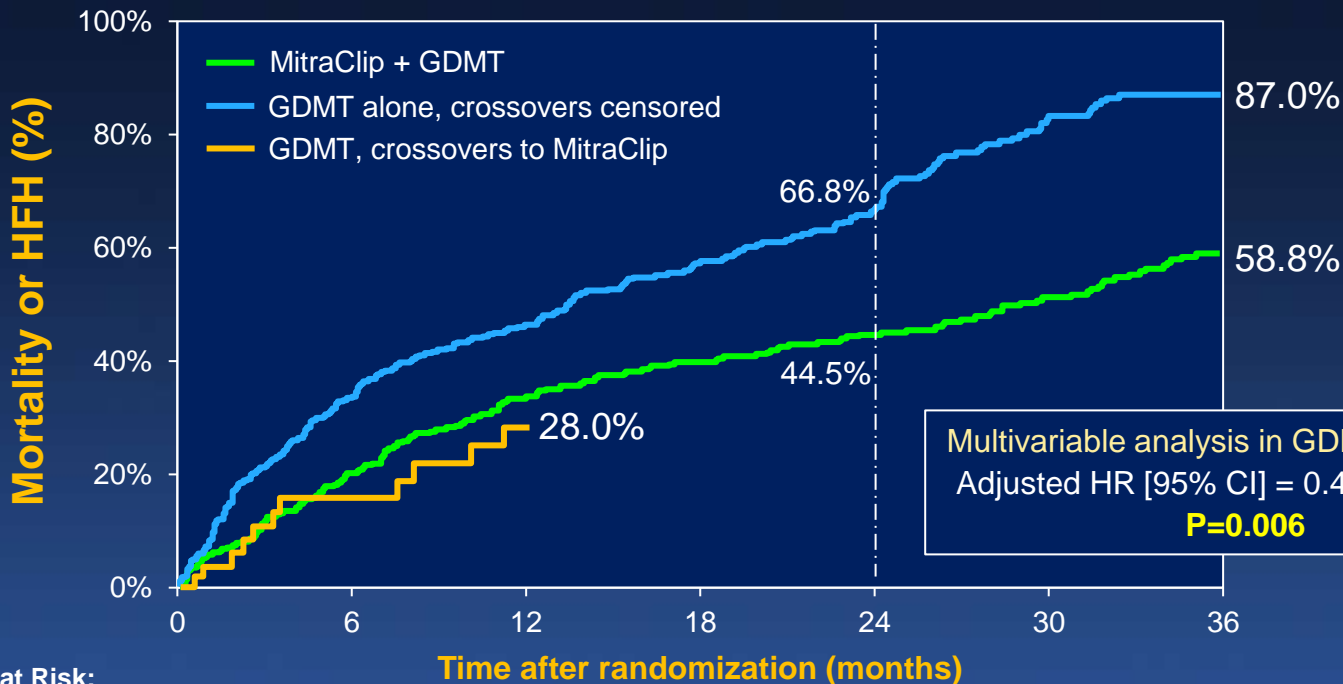


at Risk:

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

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				

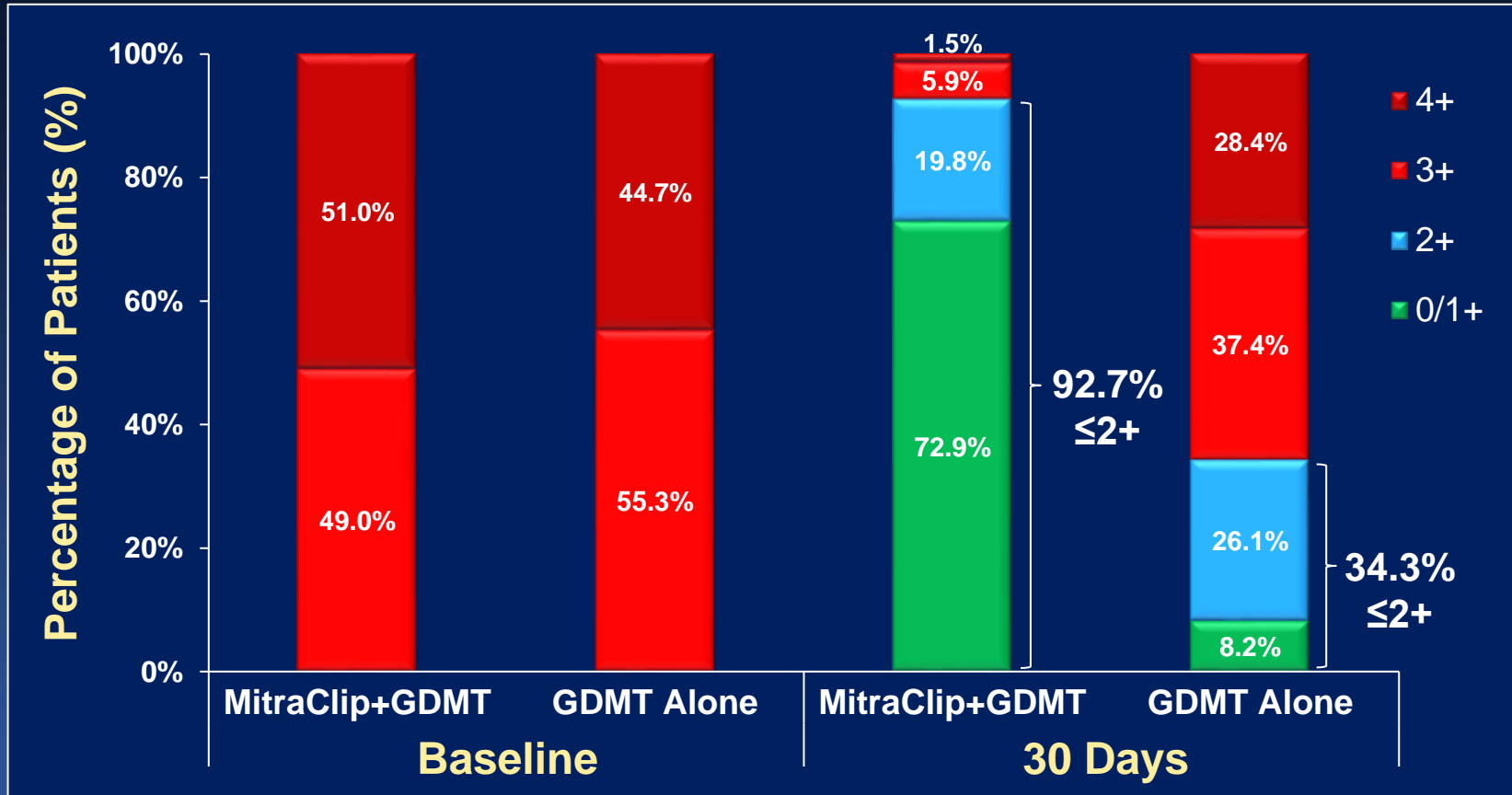
Primary Safety Endpoint (MitraClip arm)

Freedom from Device-related Complications

n=293 pts with MitraClip procedure attempted

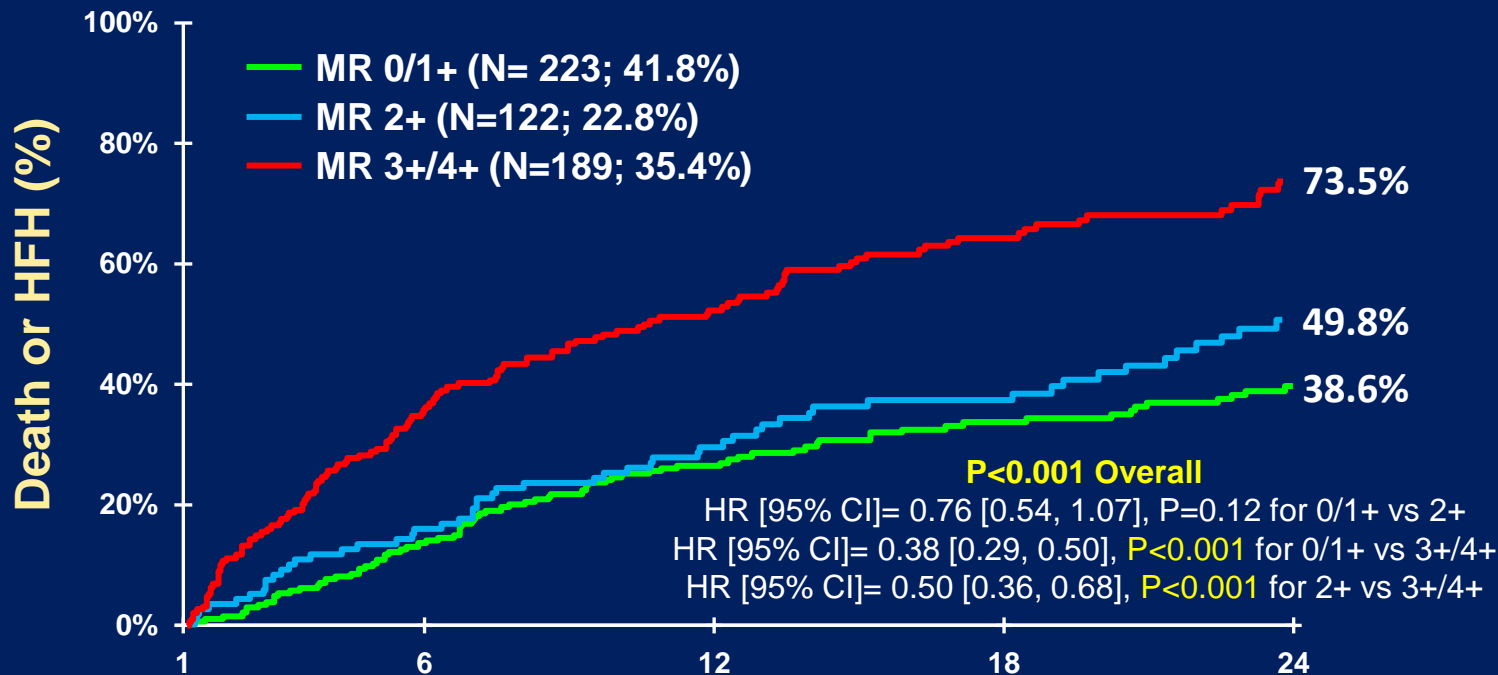
	0-30 Days	0-12 Months	0-24 Months	0-36 Months
All	1.4% (4)	3.3% (9)	5.2% (13)	8.7% (18)
- Device-related complications	1.4% (4)	1.4% (4)	1.4% (4)	1.4% (4)
• Single leaflet device attachment	0.7% (2)	0.7% (2)	0.7% (2)	0.7% (2)
• Device embolization	0.3% (1)	0.3% (1)	0.3% (1)	0.3% (1)
• Endocarditis requiring 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)

MR Reduction in COAPT



Time to Death or First HF Hosp

Pooled population, stratified by 30-day residual MR



At Risk

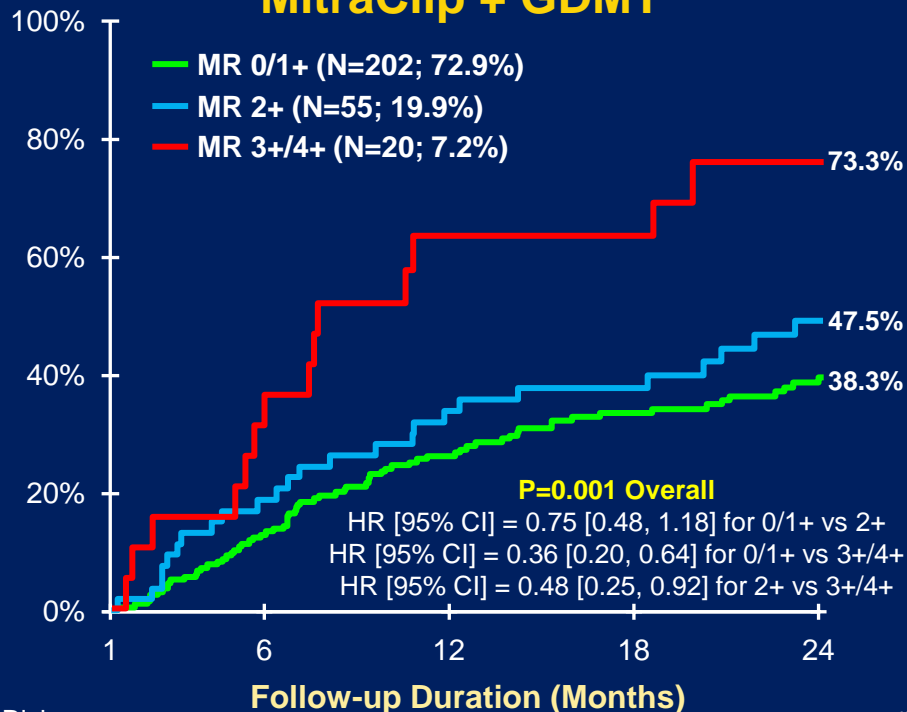
MR 0/1+	223	192	152	117	73
MR 2+	122	101	81	57	36
MR 3+/4+	189	120	83	51	30

Time to Death or First HF Hosp

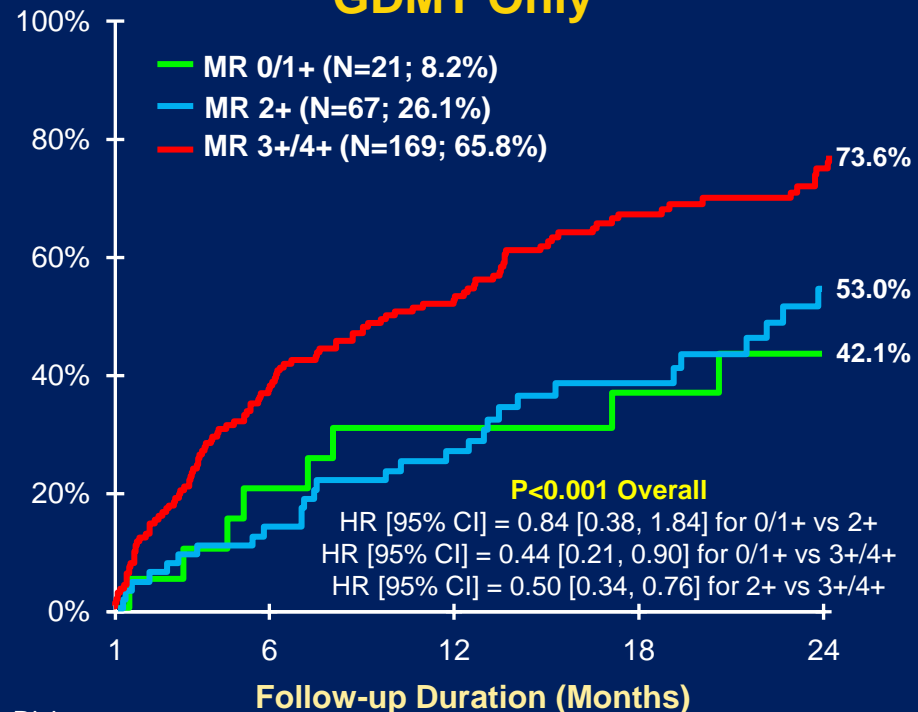
Randomization groups stratified by 30-day residual MR

$P_{int}=0.93$

MitraClip + GDMT



GDMT Only



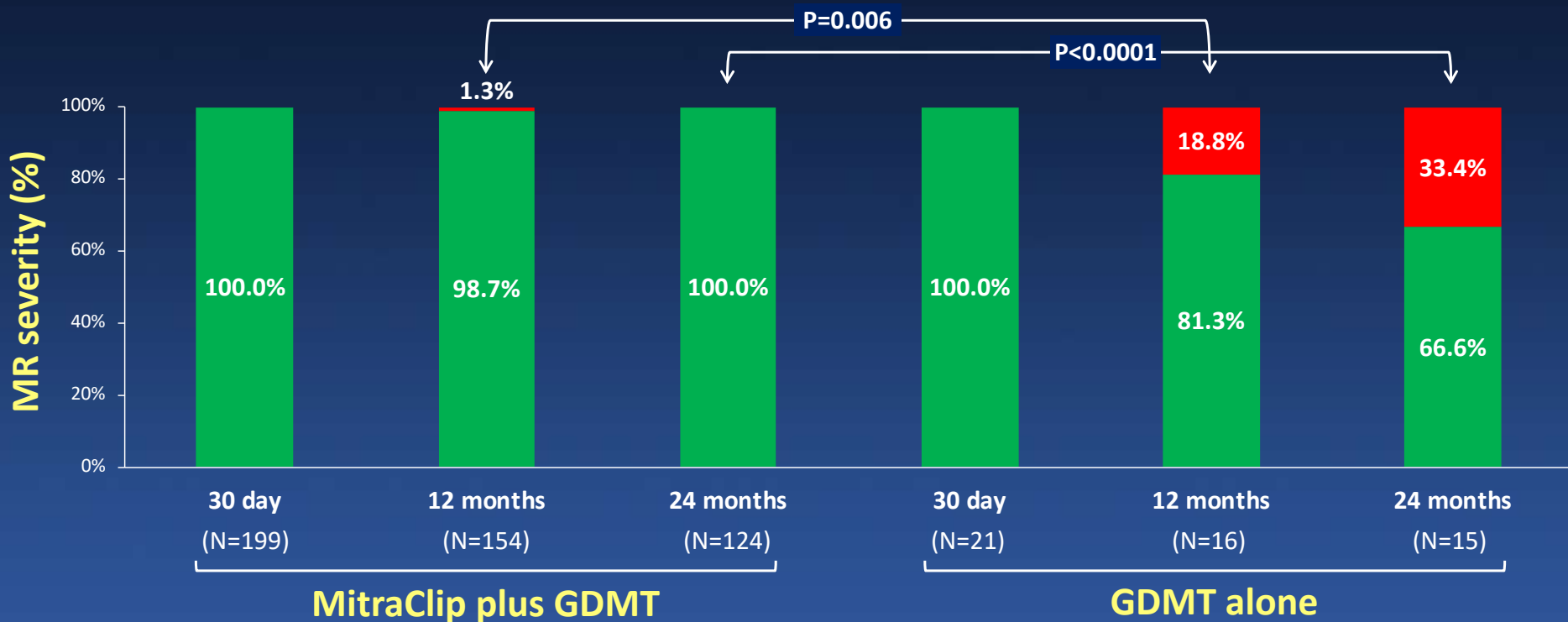
# At Risk	1	6	12	18	24
MR 0/1+	202	176	139	106	66
MR 2+	55	45	37	31	21
MR 3+/4+	20	13	7	7	4

# At Risk	1	6	12	18	24
MR 0/1+	21	16	13	11	7
MR 2+	67	56	44	26	15
MR 3+/4+	169	107	76	44	26

Stability of 30-Day MR Grade

Patients with 30-day residual MR 0/1+

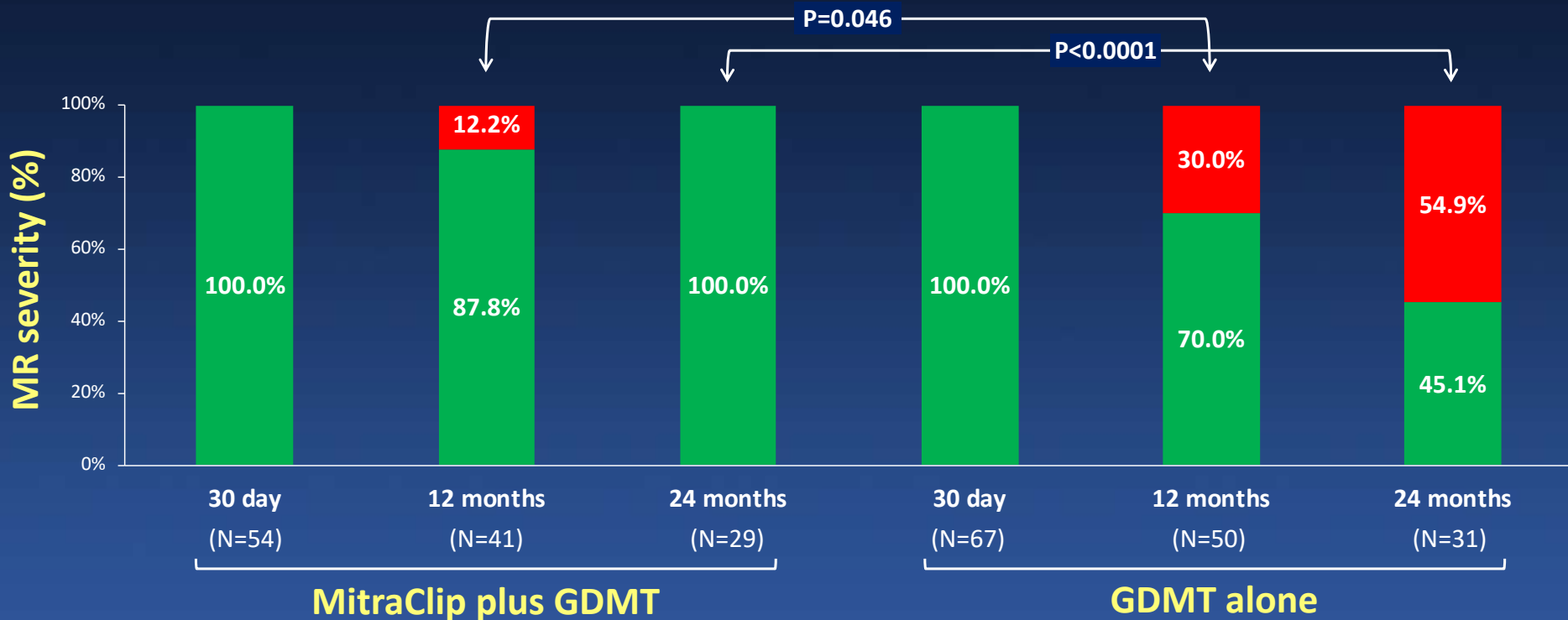
■ MR ≤2+ ■ MR >2+



Stability of 30-Day MR Grade

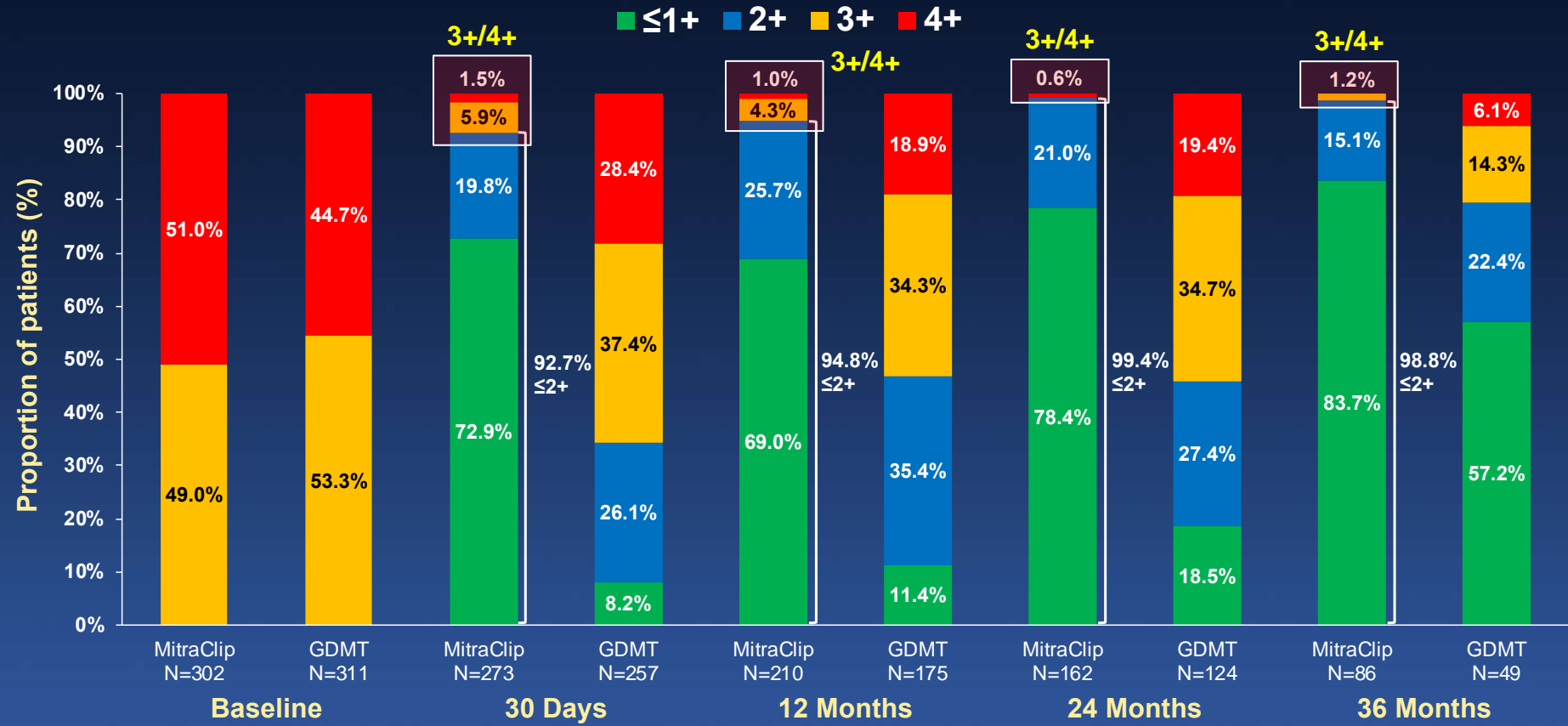
Patients with 30-day residual MR 2+

■ MR ≤2+ ■ MR >2+

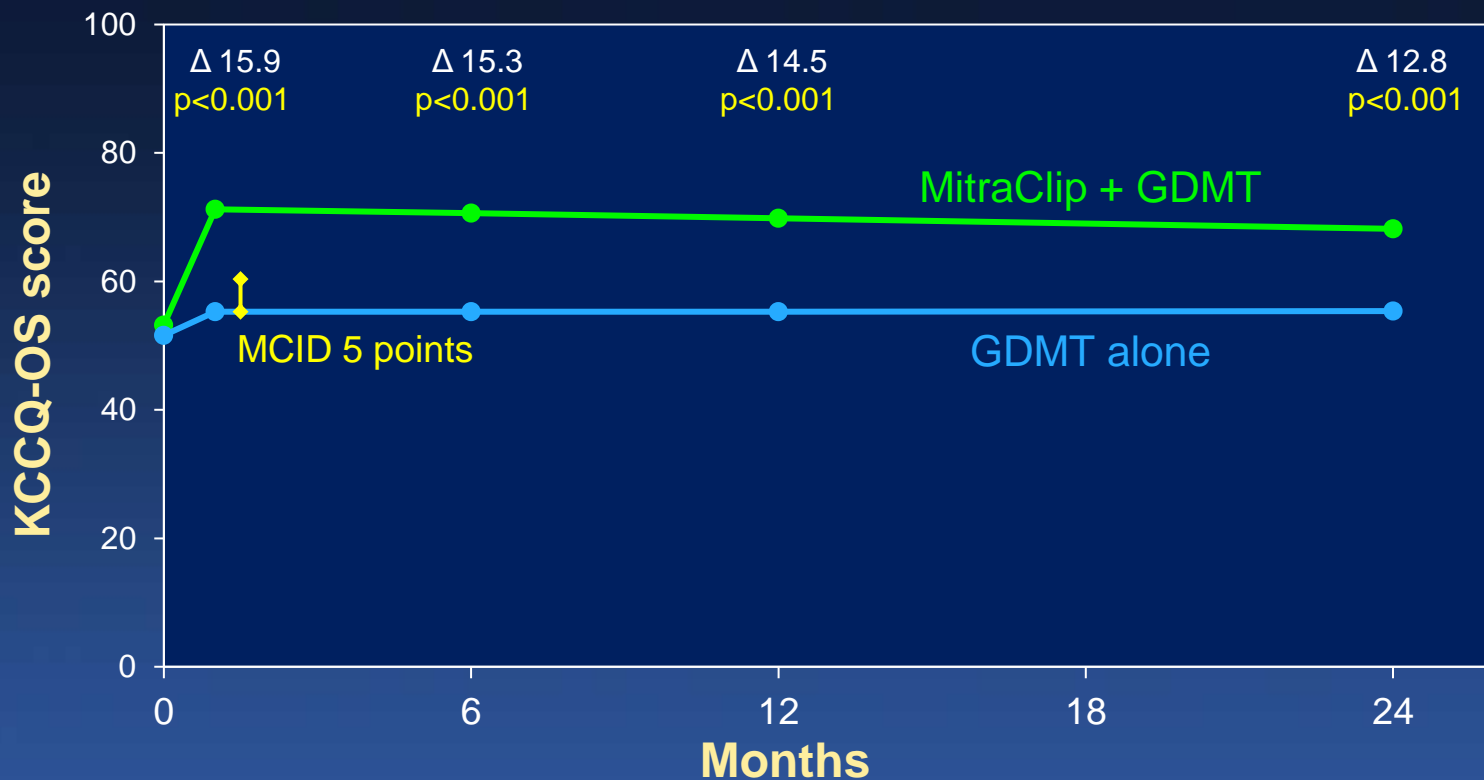


MR Severity

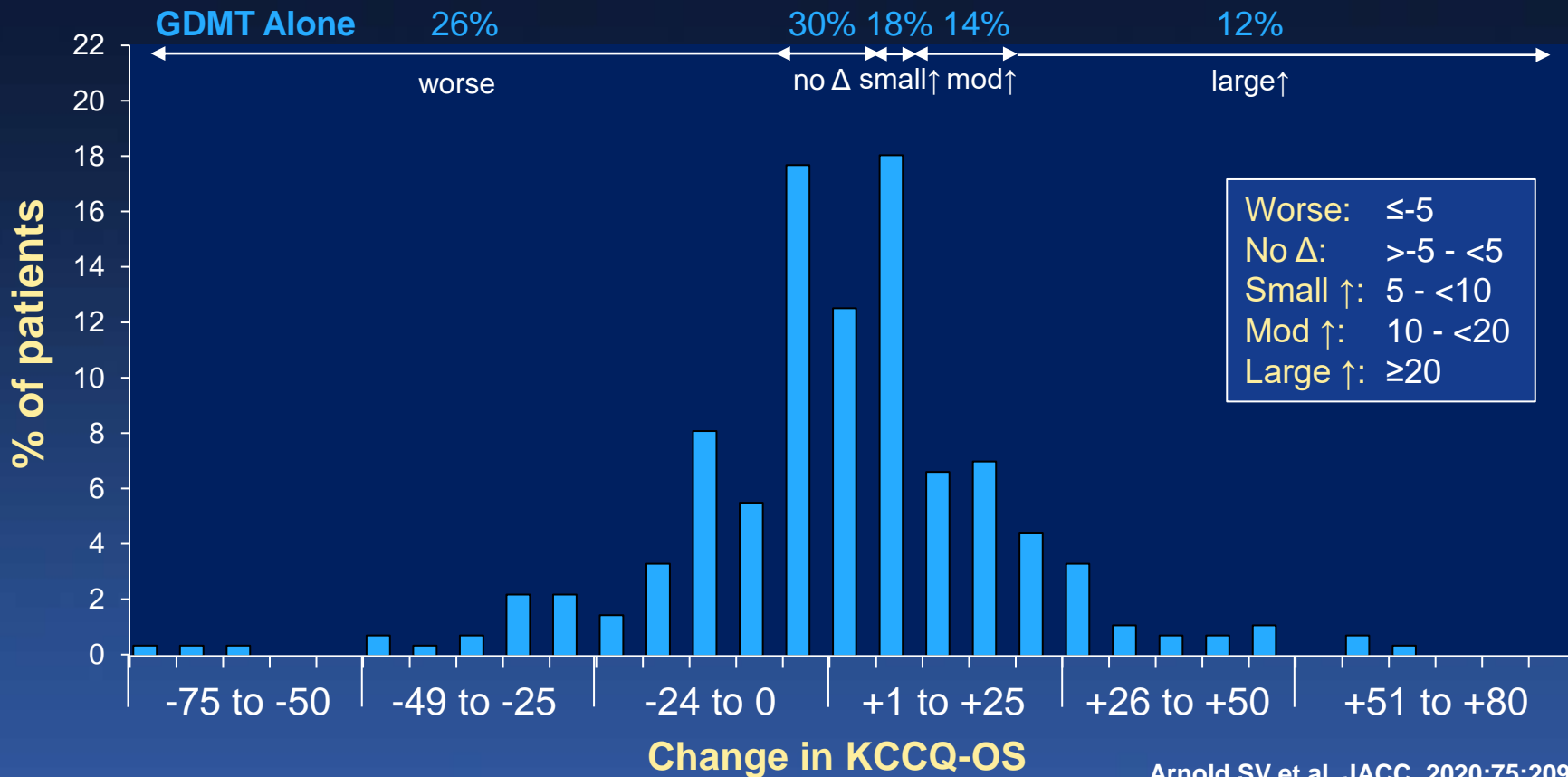
All FU P<0.0001
for trend and for ≤2+



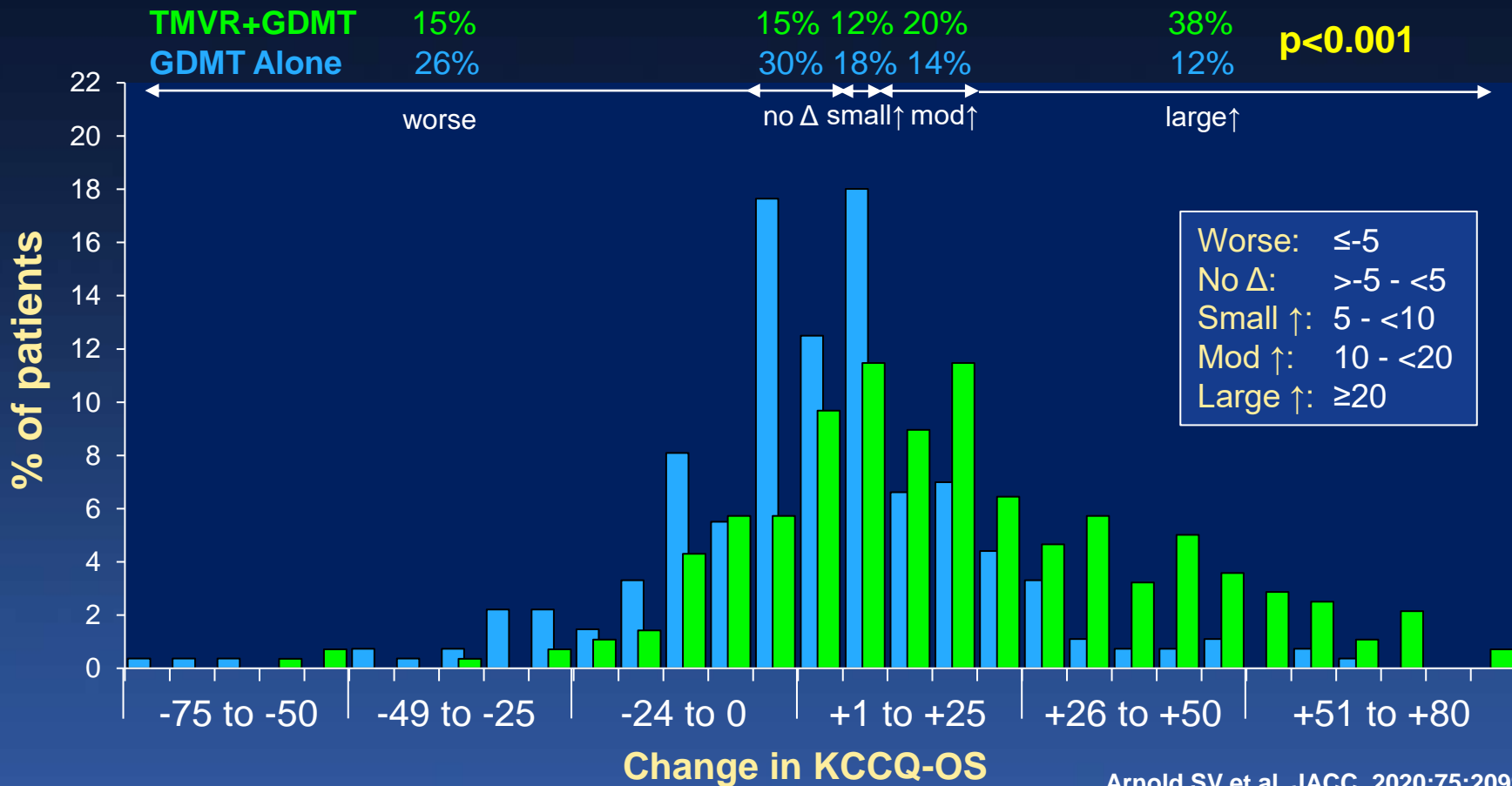
Effects of TMVr: Health Status



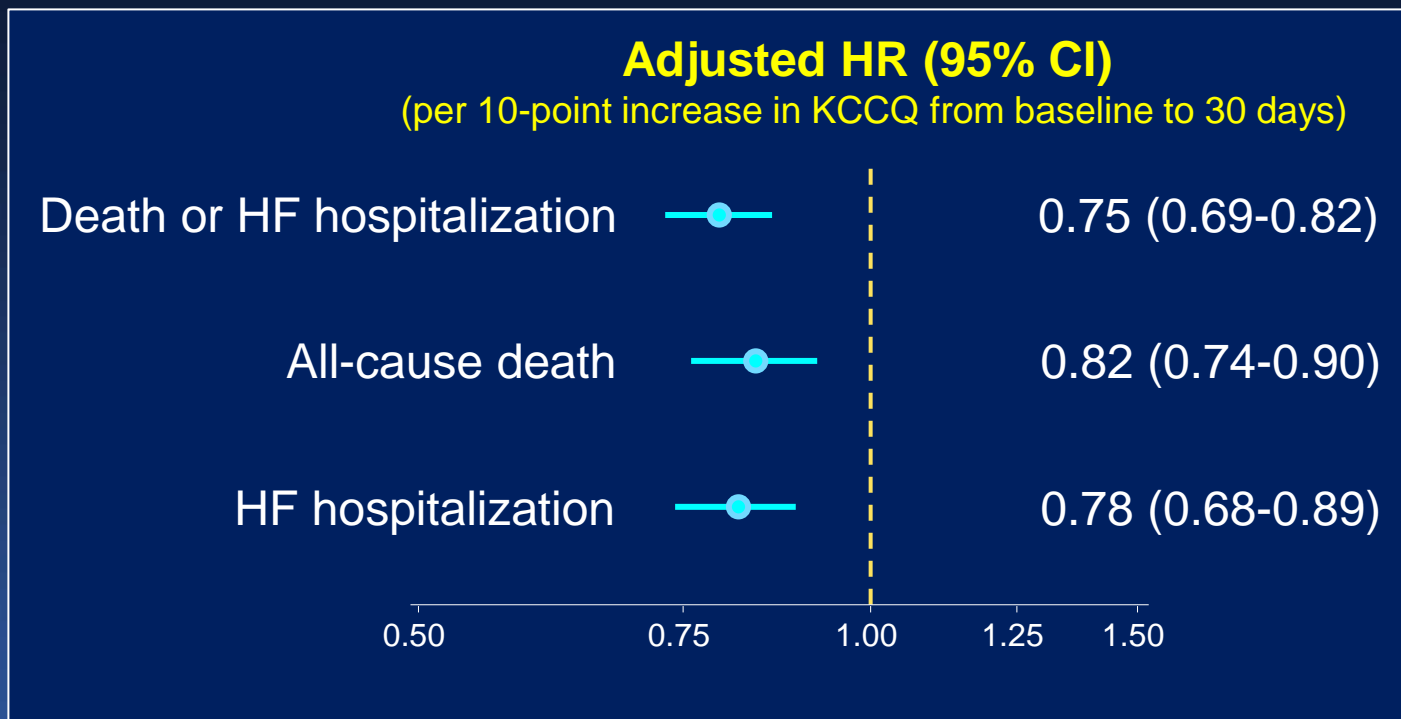
Change in KCCQ-OS at 1 Month



Change in KCCQ-OS at 1 Month



Association of 1-Month Change in KCCQ and Outcomes Between 1 Month and 2 Years

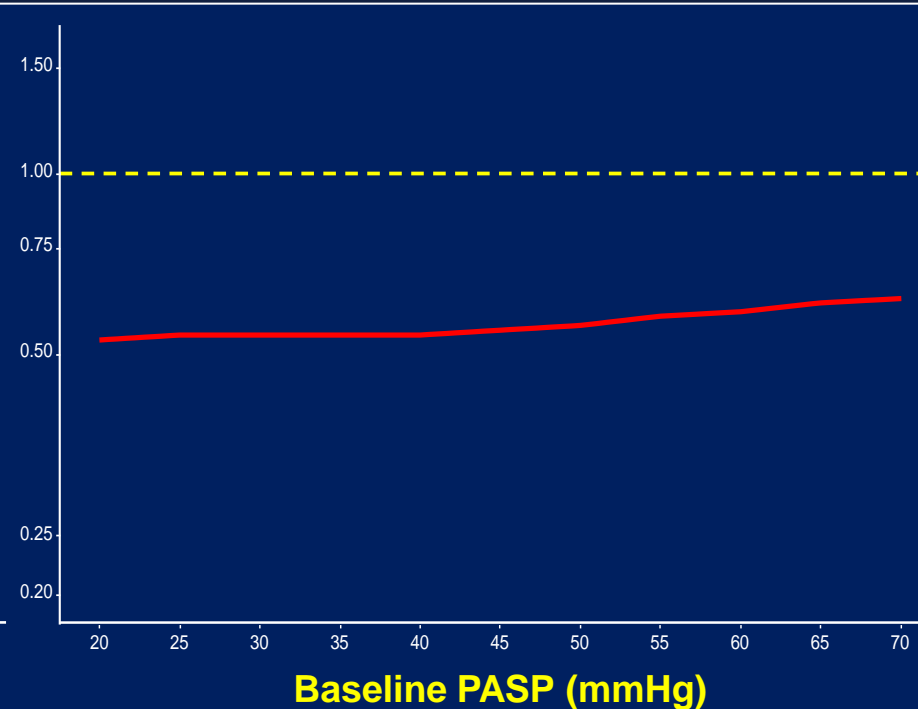
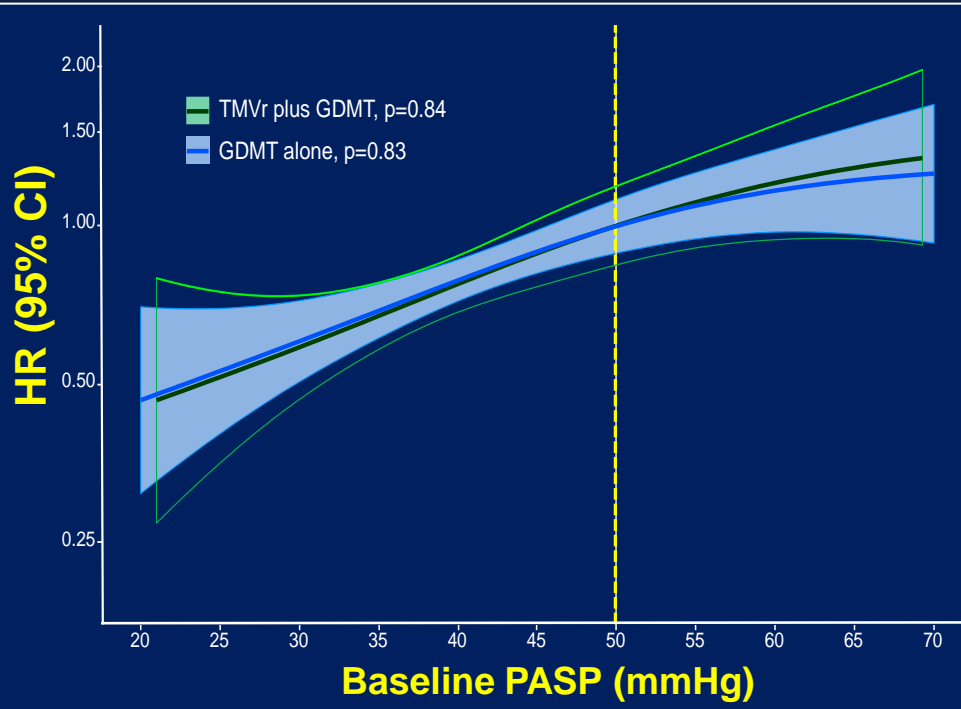


Impact of Pulmonary HTN

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

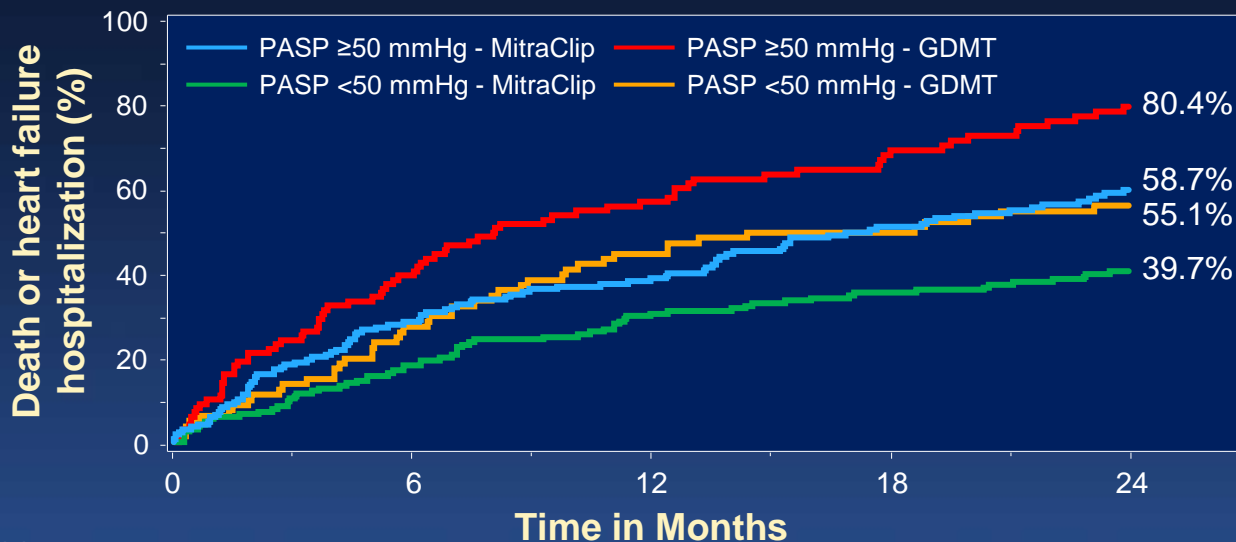
HR for MitraClip and GDMT alone separately, referenced to PASP 50 mmHg

HR for MitraClip vs. GDMT alone



Impact of Pulmonary HTN

Median PASP (echo) was 43.1 [34.0, 53.0] mmHg, range 13.0 - 112.0 mmHg



MitraClip vs GDMT:

PASP ≥50 mmHg:

HR (95%CI) =
0.54 (0.39, 0.98)

P=0.0009

PASP <50 mmHg:

HR (95%CI) =
0.59 (0.46, 0.75)

P=0.0008

P_{int} = 0.78

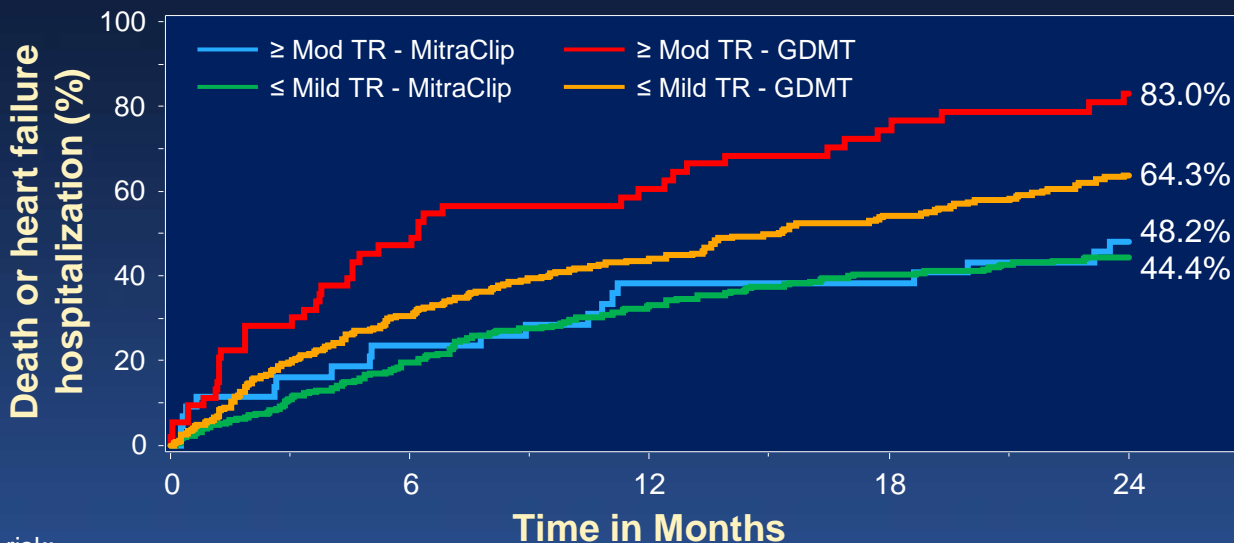
Number at risk:

	0	6	12	18	24
PASP ≥50 - MitraClip	82	60	45	41	34
PASP ≥50 - GDMT	102	61	41	30	19
PASP <50 - MitraClip	171	137	117	107	92
PASP <50 - GDMT	173	124	119	77	58

Impact of Baseline TR

TR severity: None/trace 2.0%; Mild 81.6%; Mod 15.4% Mod/sev 0.8%; Sev 0.2%

83.6% had \leq Mild TR and 16.4% had \geq ModTR



Number at risk:

\geq Mod TR - MitraClip	44	31	25	25	19
\geq Mod TR - GDMT	54	28	20	12	8
\leq Mild TR - MitraClip	255	204	169	149	129
\leq Mild TR - GDMT	246	170	129	102	74

MitraClip vs GDMT:

In pts with \geq Mod TR:

HR (95%CI) =
0.40 (0.23, 0.68)

P=0.0005

In pts with \leq Mild TR:

HR (95%CI) =
0.59 (0.46, 0.75)

P<0.0001

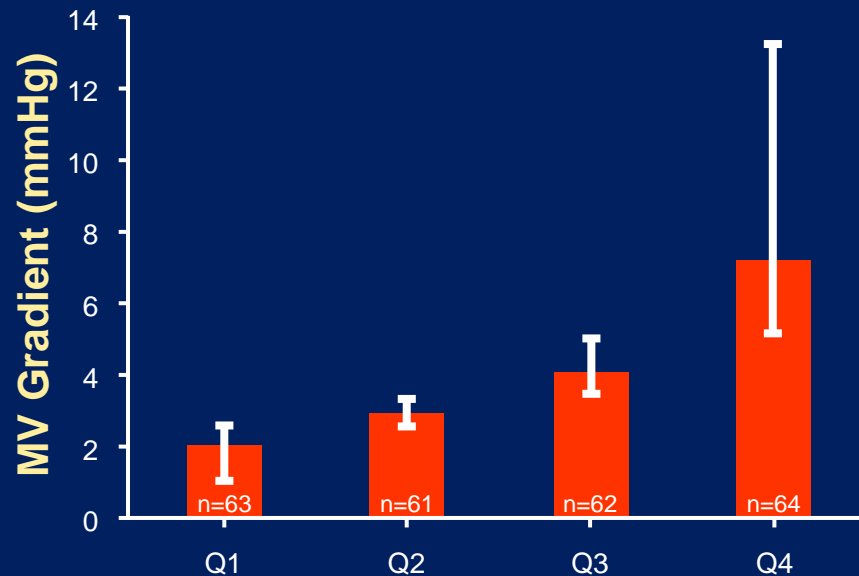
P_{int} = 0.16

Impact of Post-MitraClip Gradient

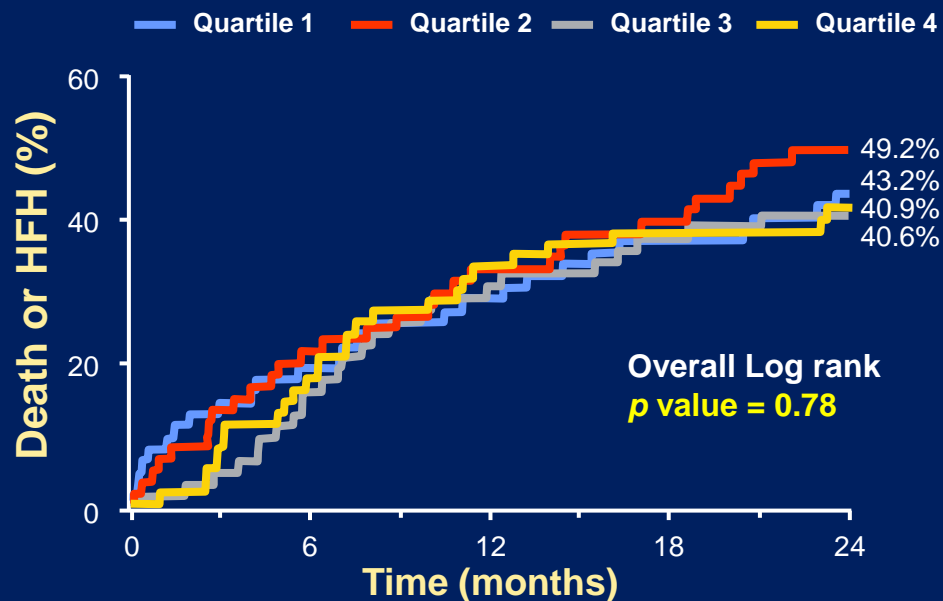
Mean discharge TTE MVG after MitraClip was 4.2 ± 2.2 mmHg (range 1 to 13.2 mmHg)*

Mean MVG in quartiles: 2.1 ± 0.4 , 3.0 ± 0.2 , 4.2 ± 0.5 , and 7.2 ± 2.0 mmHg

Mitral Valve Gradient by Quartile



Death or HF Hospitalization

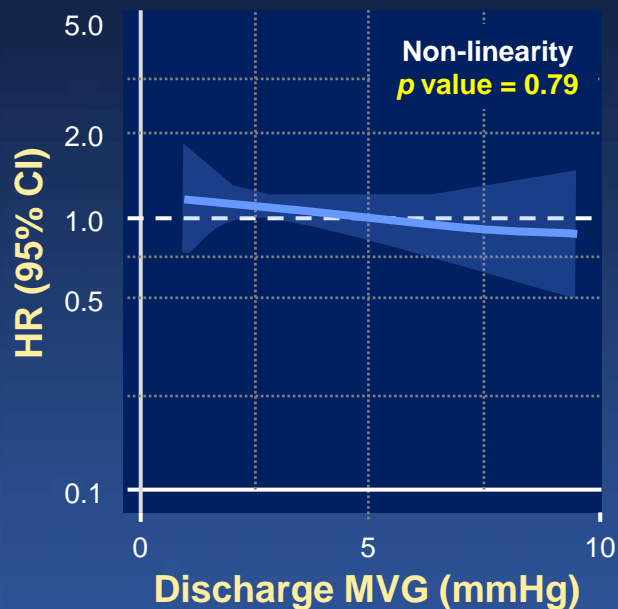


Impact of Post-MitraClip Gradient

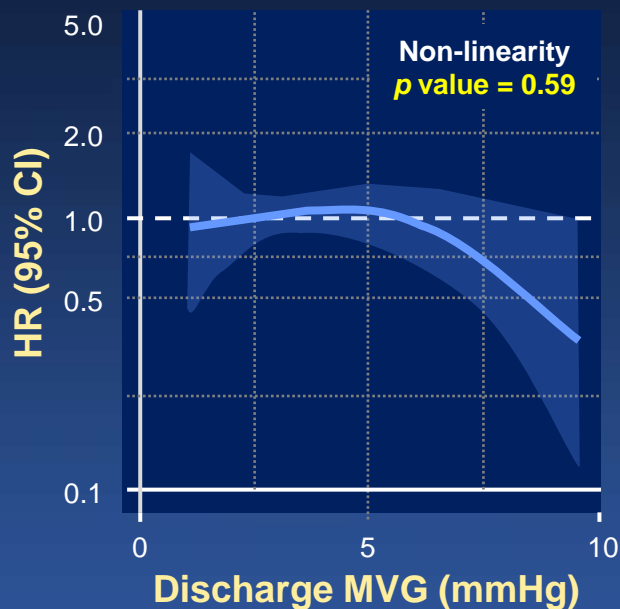
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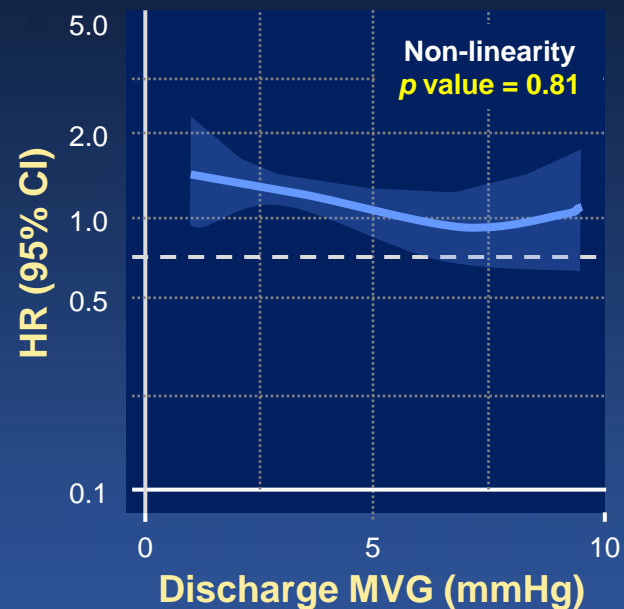
Death or HFH



Death



HFH



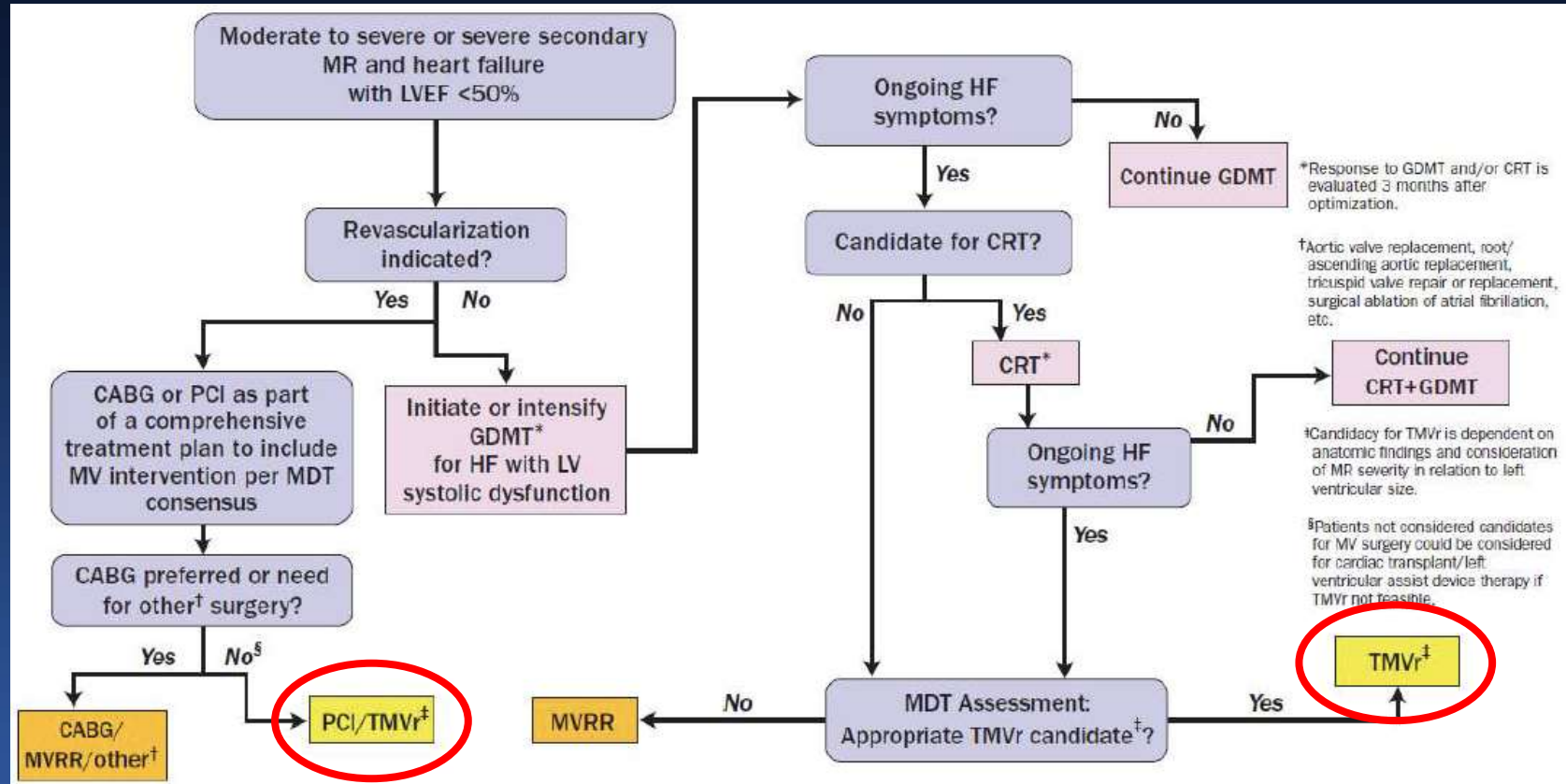
March 14th, 2019

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.

Intervention for Symptomatic Secondary MR

2020 Focused Update of the 2017 ACC Expert Consensus Decision Pathway for MR



Ascent to Widespread Utilization

Evidence generation
(COAPT) ✓

FDA approval/
indication ✓

Guidelines
adoption ✓

CMS reimbursement



Heart team organization
(HF, Im, Card, IC, CTS)

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Improved nationwide
outcomes for
HF pts with severe MR

