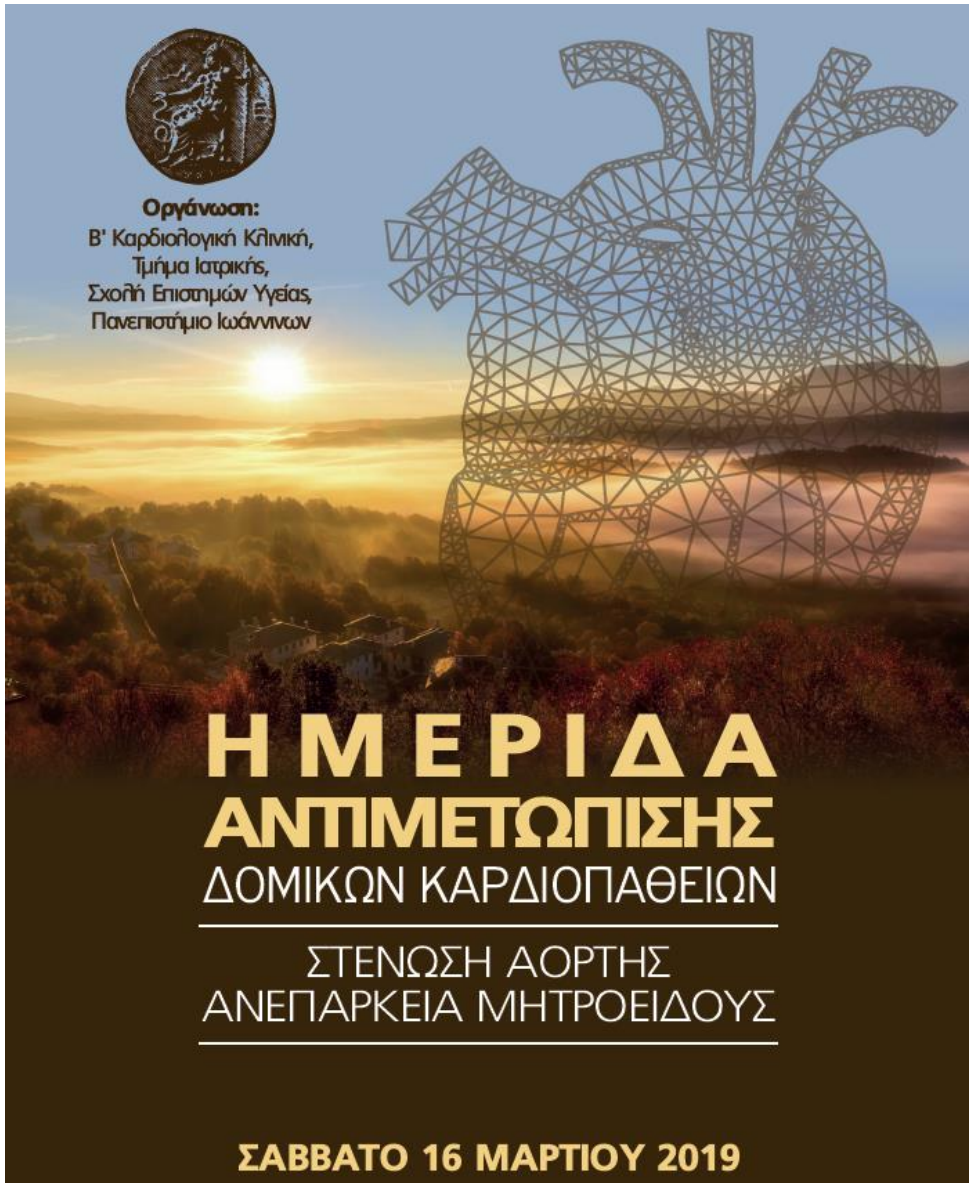


Ανεπάρκεια Μιτροειδούς
Mitral Regurgitation (MR)

Διαδερμική Θεραπεία MR σε Ασθενή με Καρδιακή Ανεπάρκεια: Ευρήματα των Πρόσφατων Μελετών MITRA-FR & COAPT

Κατερίνα Κ. Νάκα MD, PhD(UK), FESC
Αναπληρώτρια Καθηγήτρια Καρδιολογίας
Ιατρική Σχολή, Πανεπιστήμιο Ιωαννίνων
Β΄ Καρδιολογική Κλινική ΠΓΝΙ

DISCLOSURES

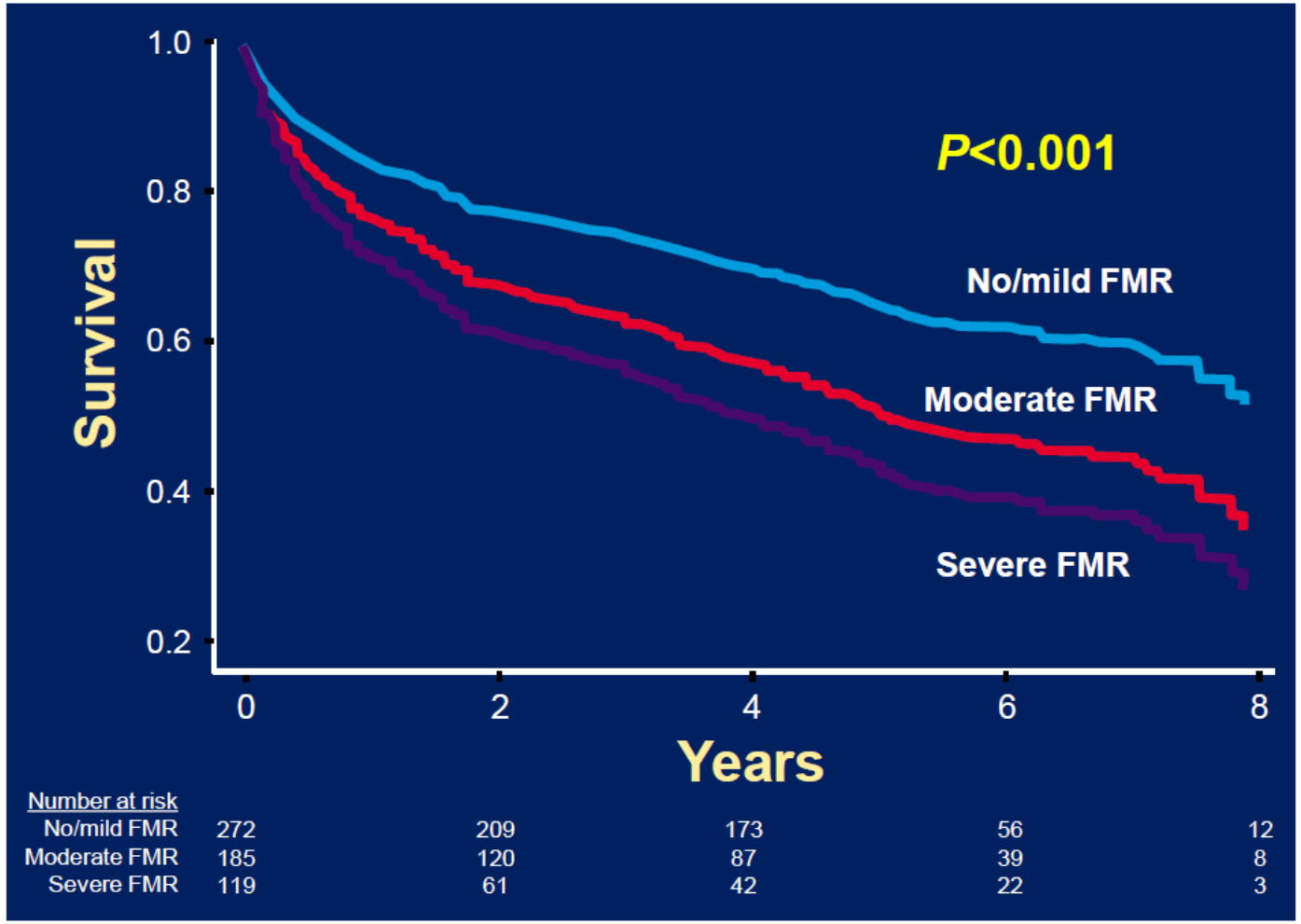
SPEAKER: KATERINA K. NAKA MD, PhD, FESC

RCTs, Registries - *Novartis, Merck, Amgen, Pfizer, Actelion, BMS, Boehringer*

Lectures – *Novartis, ΕΛΠΕΝ*

Horizon2020 funding – *KardiaTool, Insilc projects*

Poorer prognosis in HFrEF
With increasing severity of functional MR

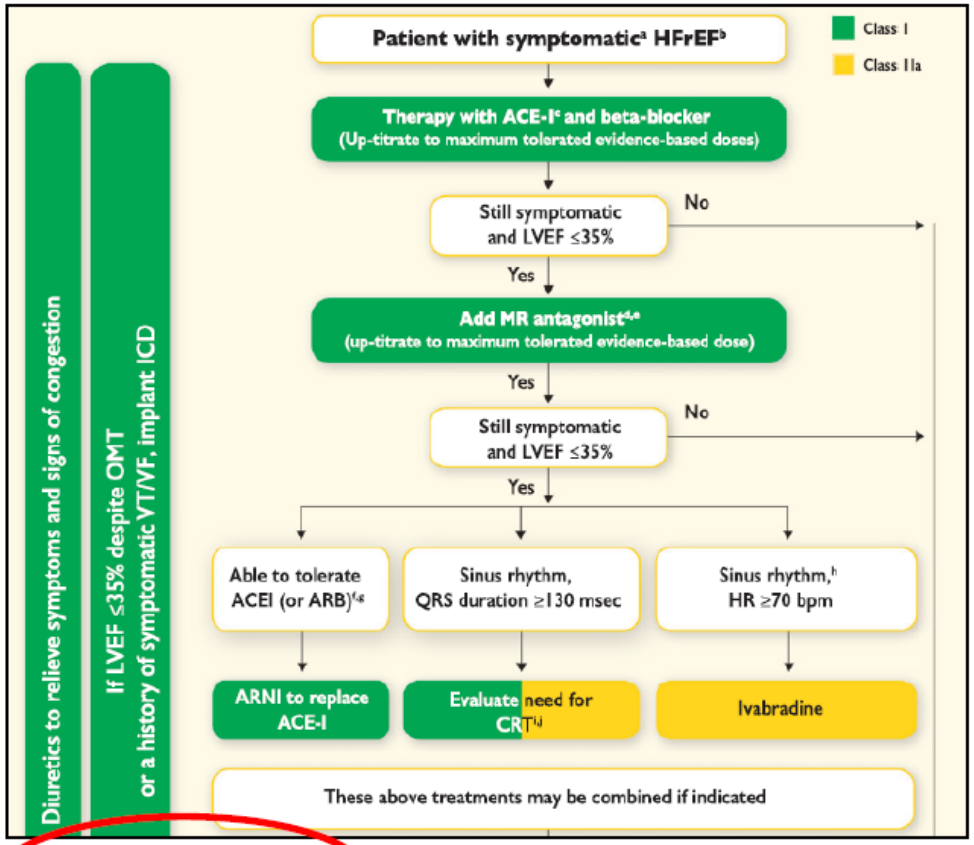


- Prospective study of 576 pts with HFrEF
- 47% died during median 5-year FU
  - severe FMR in 21%
  - mod FMR in 32%

- Severe secondary MR is an independent predictor of long-term mortality after multivariable adjustment for clinical, echo, biomarker and medication variables

Goliasch G et al. *EHJ* 2018;39:39-46

Current guidelines for HFrEF management



Medical therapy for patients with symptomatic heart failure with reduced ejection fraction

COR Class I, LOE A

[1] Ponikowski P. European Heart Journal (2016) 37, 2129–2200

Recommendations for ICD/CRT Use	COR	LOE
ICD to reduce the risk of sudden death and all-cause mortality in HF patients with expected survival > 1-year with good functional status		
• ICD for primary prevention in patient with symptomatic HF (NYHA Class II–III), and an LVEF ≤35% despite ≥3 months of OMT, and have Ischemic heart disease (A) and dilated cardiomyopathy (B)	I	A,B
• ICD for secondary prevention in patients recovering from ventricular arrhythmia causing hemodynamic instability	I	A
CRT is recommended for symptomatic HF patients with LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality, and in sinus rhythm with	I	
• a QRS duration ≥150 msec	I	A
• a QRS duration 130-149 msec	I	B
CRT rather than RV pacing for patients with HFrEF regardless of NYHA class but indicated for ventricular pacing and high degree AV block in order to reduce morbidity. Includes AF patients	I	A

And what about functional MR in HFrEF ?

Combined surgery of secondary mitral regurgitation and coronary artery bypass grafting should be considered in symptomatic patients with LV systolic dysfunction (LVEF <30%), requiring coronary revascularization for angina recalcitrant to medical therapy.	IIa	C
Isolated surgery of non-ischaemic regurgitant mitral valve in patients with severe functional mitral regurgitation and severe LV systolic dysfunction (LVEF <30%) may be considered in selected patients in order to avoid or postpone transplantation.	IIb	C

In patients with HF with moderate-severe secondary MR
who are judged **inoperable or at high surgical risk**
percutaneous MV intervention **(percutaneous edge-to-edge repair) may be considered**
in order to improve symptoms and quality of life,
although no RCT evidence of improvement has been published, only registry studies

- Meta-analysis
- European registry
- German registry

Ponikowski et al, ESC guidelines on HF 2016

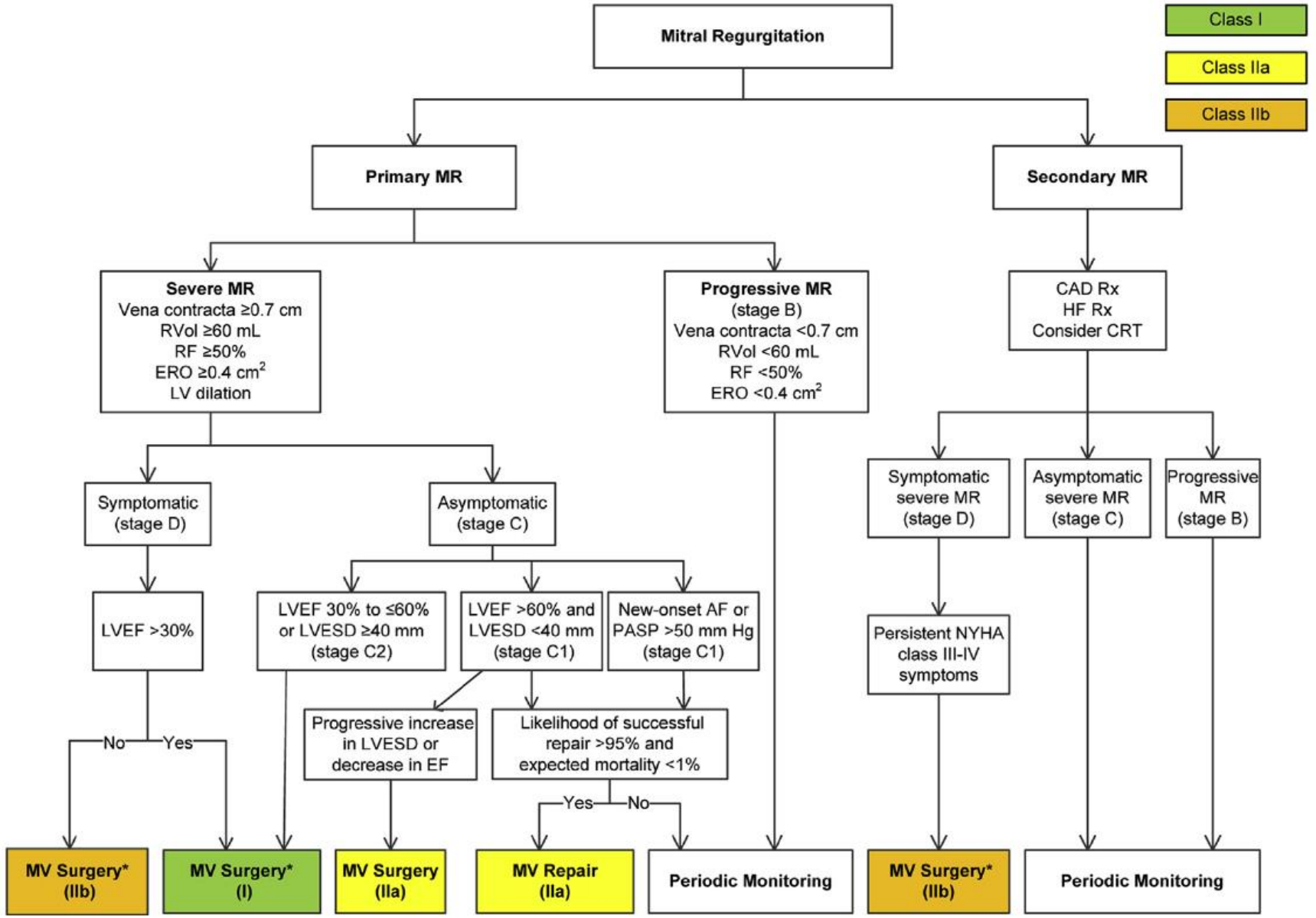
Recommendations for secondary MR intervention

Indications for mitral valve intervention in chronic secondary mitral regurgitation[a]

Recommendations	Class[b]	Level[c]
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 optimal medical management (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 optimal medical management (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 optimal medical management (including CRT if indicated) and who have no option for revascularization, the Heart Team may consider a percutaneous edge-to-edge procedure or valve surgery after careful evaluation for a ventricular assist device or heart transplant according to individual patient characteristics.	IIb	C

Baumartner et al, ESC guidelines on VHD 2017

FIGURE 2 Indications for Surgery for MR (Updated Figure 4 From the 2014 VHD guideline)



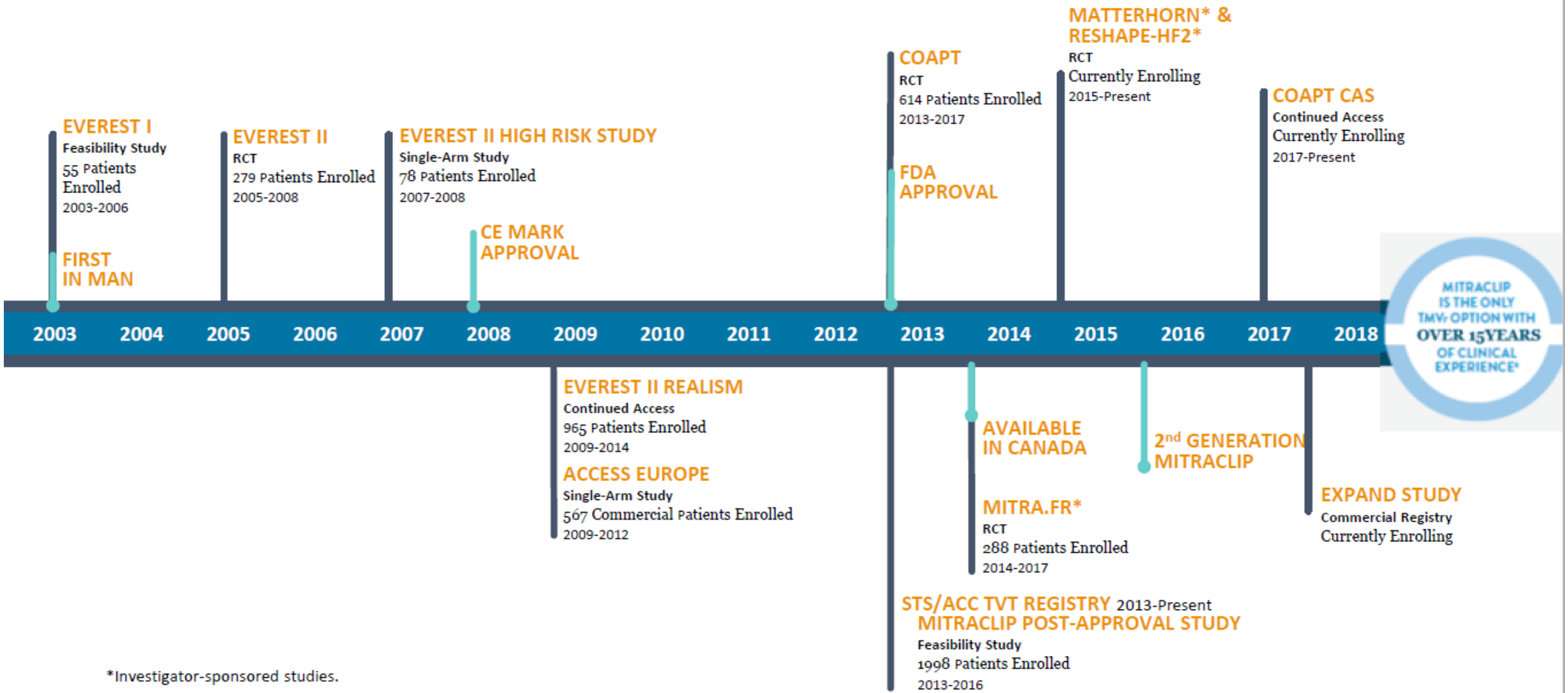
Nishimura et al, ACC/AHA update on VHD guidelines 2017

Recommendations for secondary MR intervention

COR	LOE	RECOMMENDATIONS	COMMENT/RATIONALE
IIa	C	Mitral valve surgery is reasonable for patients with chronic severe secondary MR (stages C and D) who are undergoing CABG or AVR.	2014 recommendation remains current.
IIa	B-R	See Online Data Supplement 18 (Updated From 2014 VHD Guideline)	**Percutaneous MV repair provides a less invasive alternative to surgery but is not approved for clinical use for this indication in the US (70,72,125–127).**
IIb	B		**The results of RCTs examining the efficacy of percutaneous MV repair in patients with secondary MR are needed to provide information on this patient group (128,129).**
IIb	B-R	See Online Data Supplement 18 (Updated From 2014 VHD Guideline)	of mitral repair in this population of patients, with increased risk of postoperative complications.

Nishimura et al, ACC/AHA update on VHD guidelines 2017

MitraClip™ Worldwide Clinical experience



*Investigator-sponsored studies.

An Established Therapy With Clinical & Real World Global Experience

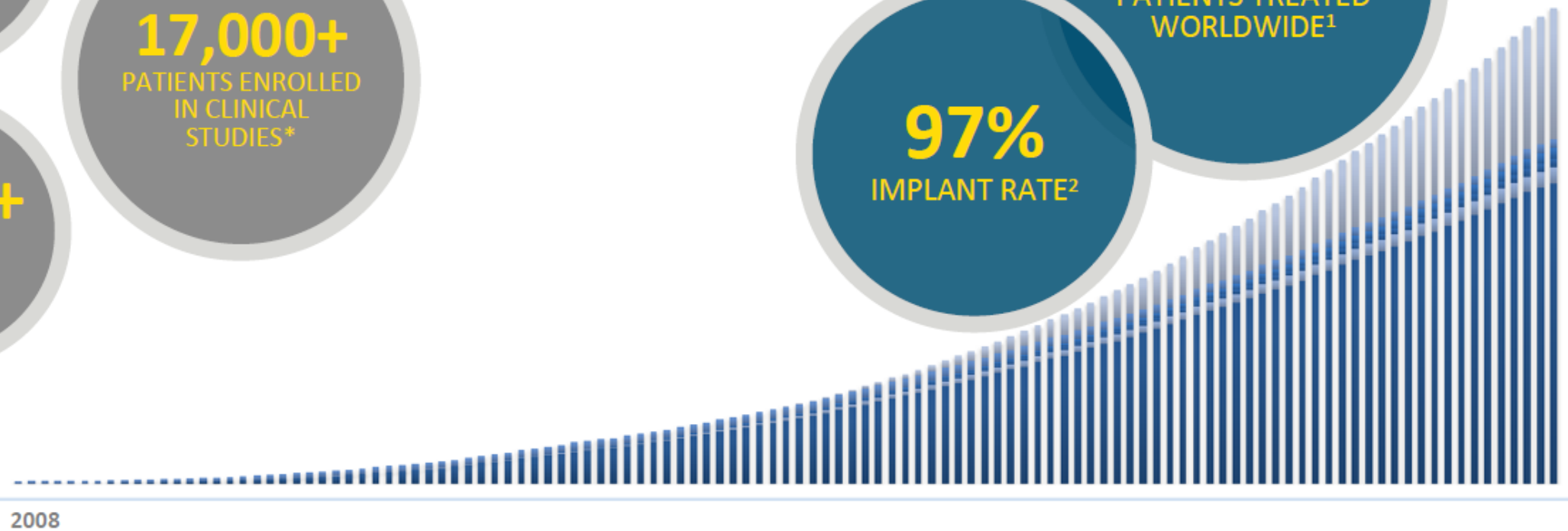
1000+
CENTERS IN 50 COUNTRIES*

17,000+
PATIENTS ENROLLED IN CLINICAL STUDIES*

1000+
PUBLISHED ARTICLES*

70,000+
PATIENTS TREATED WORLDWIDE[1]

97%
IMPLANT RATE[2]



Cumulative Global MitraClip® Experience

New RCT results for MitraClip Therapy in secondary MR in HF patients

Two RCTs Reported Primary Results in 2018 evaluating MitraClip + GDMT against GDMT alone

Mitra-FR

- Sponsored by Investigators and funded by French Ministry of Health
- MR severity defined per European guidelines
- published in NEJM.org

Mitra.fr

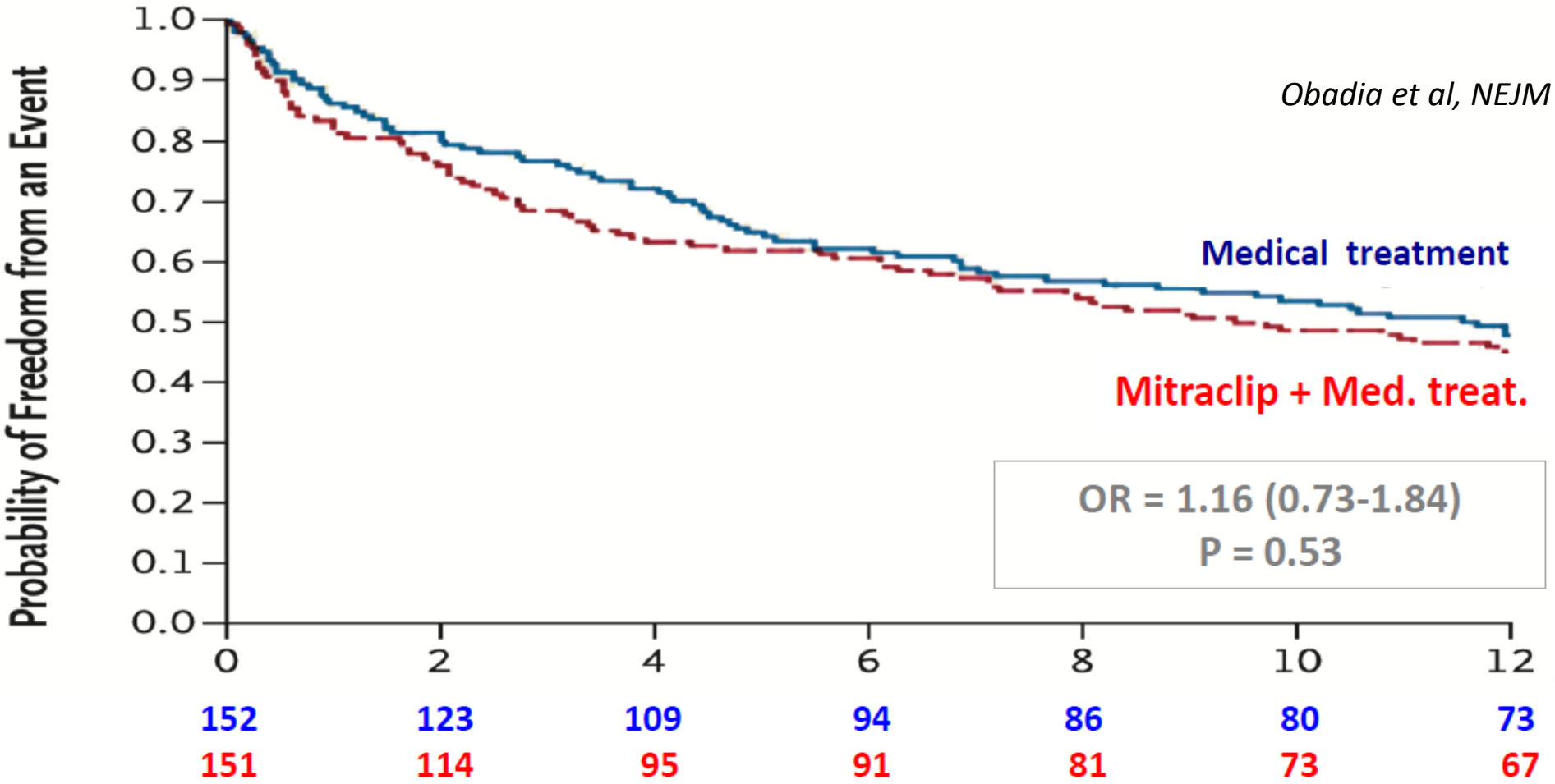
COAPT

- Sponsored by Abbott and designed in partnership with FDA and study PI's to seek an FMR indication approval
- MR severity defined per ACC/ASE guidelines
- published in NEJM.org

COAPT TRIAL

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

- All-Cause Death
- Unplanned rehospitalization for HF

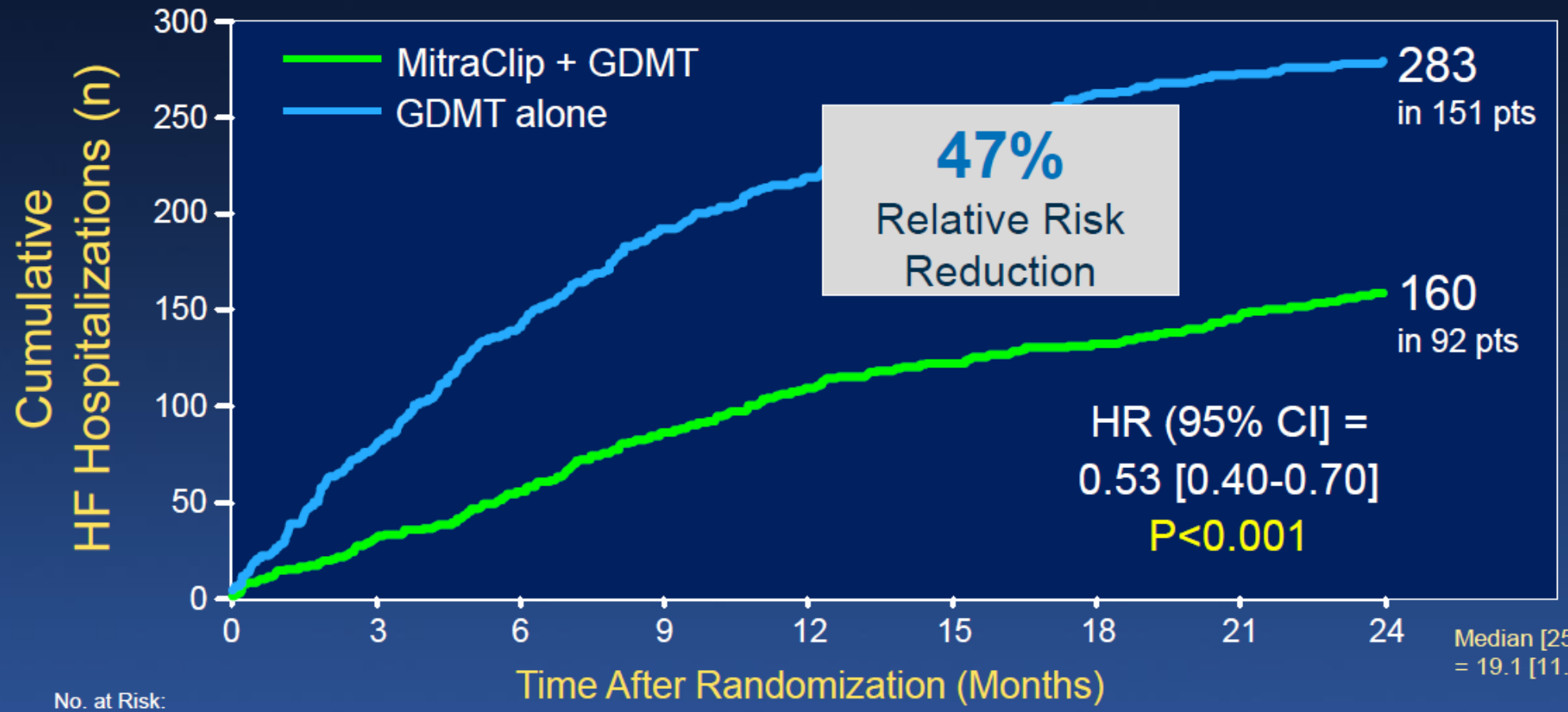


Obadia et al, NEJM Aug 2018

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

Powered Secondary Endpoints

- Tested in hierarchical order[1] -

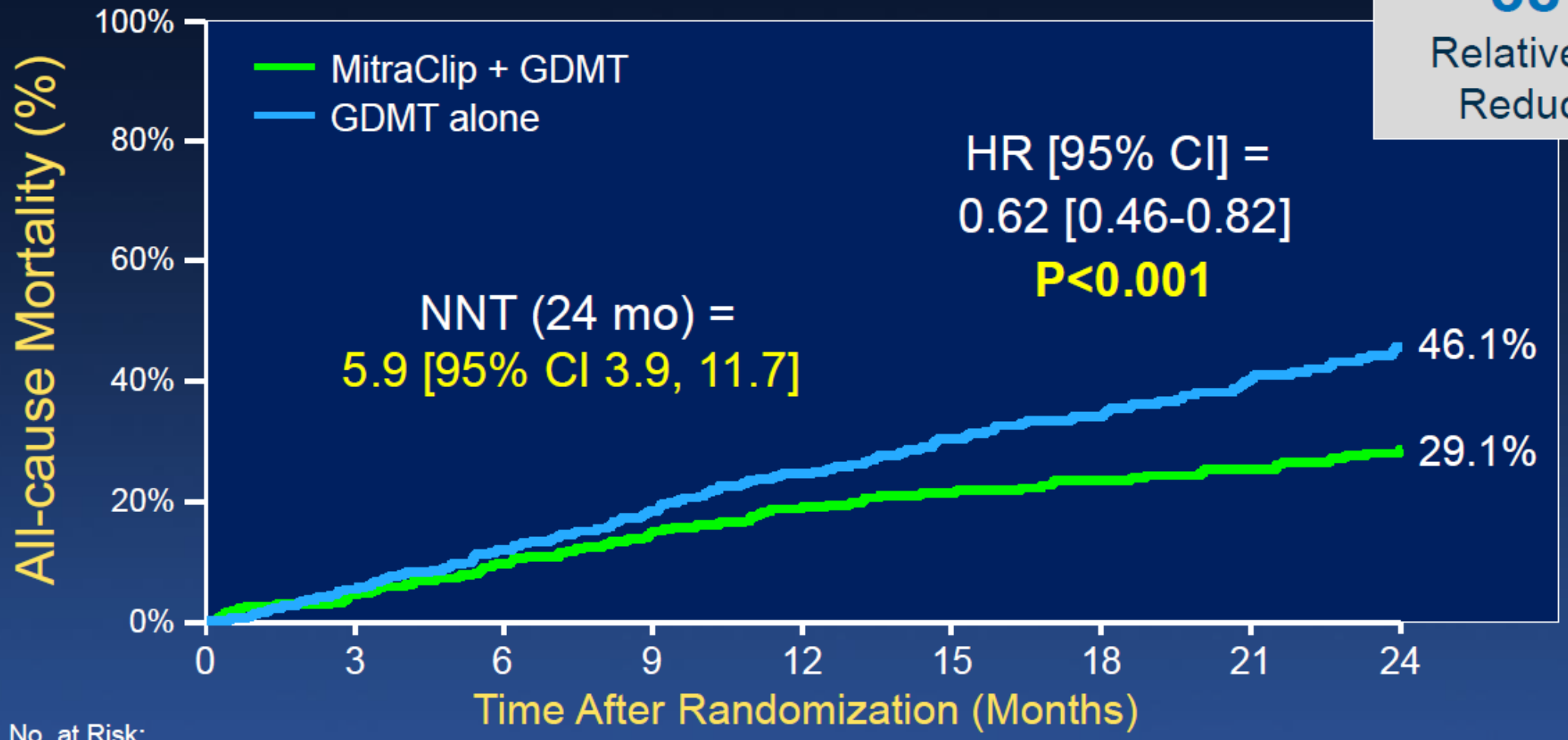
	P-value
1. MR grade ≤2+ at 12 months	<0.001
2. All-cause mortality at 12 months[2]	<0.001
3. Death and all HF hospitalization through 24 months (Finkelstein-Schoenfeld)	<0.001
4. Change in QOL (KCCQ) from baseline to 12 months	<0.001
5. Change in 6MWD from baseline to 12 months	<0.001
6. All-cause hospitalizations 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

Stone GW et al. TCT 2018

COAPT TRIAL

All-cause Mortality



38%
Relative Risk Reduction

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

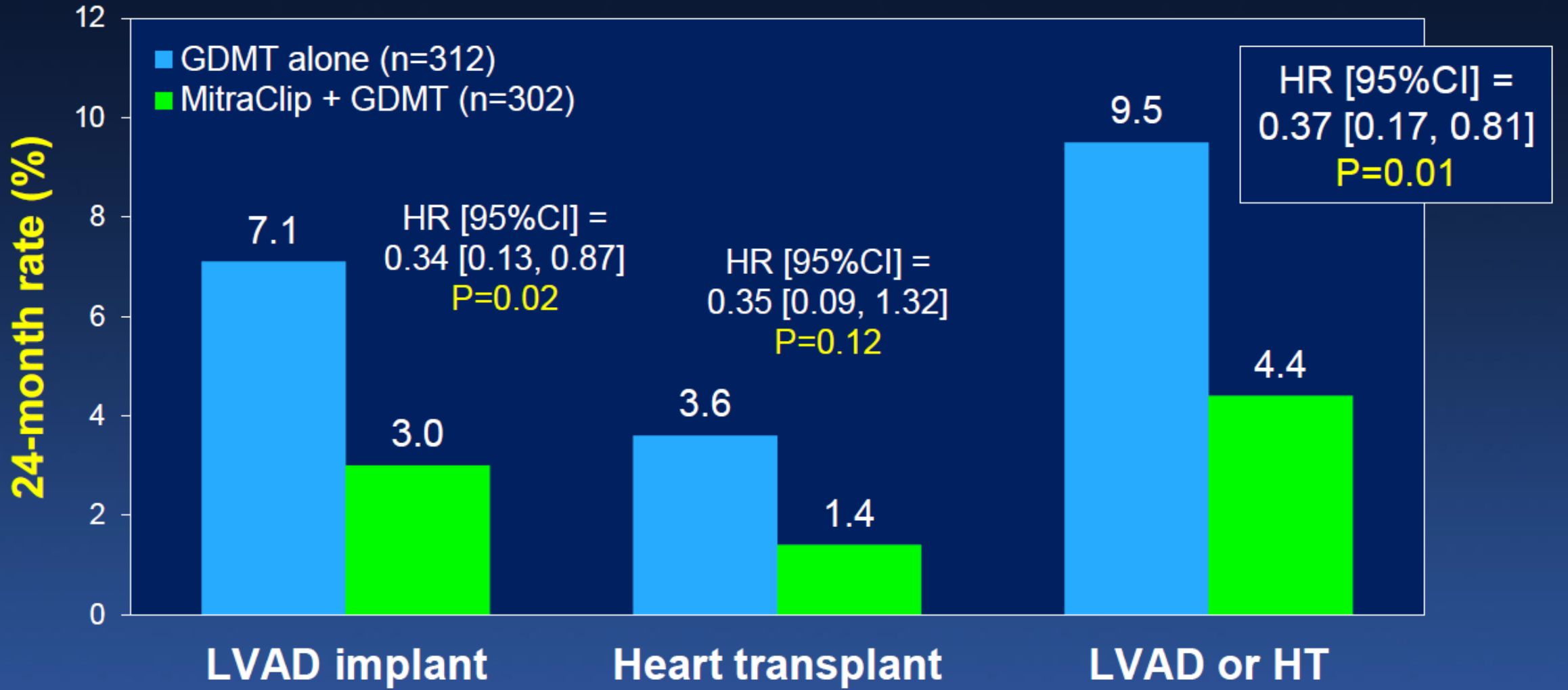
24-Month Event Rates (i)

	MitraClip + GDMT (n=302)	GDMT alone (n=312)	HR [95% CI]	P-value
Death, all-cause	29.1%	46.1%	0.62 [0.46, 0.82]	<0.001
- CV	23.5%	38.2%	0.59 [0.43, 0.81]	<0.001
- HF-related	12.0%	25.9%	0.43 [0.27, 0.67]	<0.001
- Non-HF-related	13.1%	16.6%	0.86 [0.54, 1.38]	0.53
- Non-CV	7.3%	12.7%	0.73 [0.40, 1.34]	0.31
Hospitalization, all-cause	69.6%	81.8%	0.77 [0.64, 0.93]	0.01
- CV	51.9%	66.5%	0.68 [0.54, 0.85]	<0.001
- HF-related	35.7%	56.7%	0.52 [0.40, 0.67]	<0.001
- Non-HF-related	29.4%	31.0%	0.98 [0.71, 1.36]	0.92
- Non-CV	48.2%	52.9%	0.91 [0.71, 1.17]	0.47
Death or HF hospitalization	45.7%	67.9%	0.57 [0.45, 0.71]	<0.001

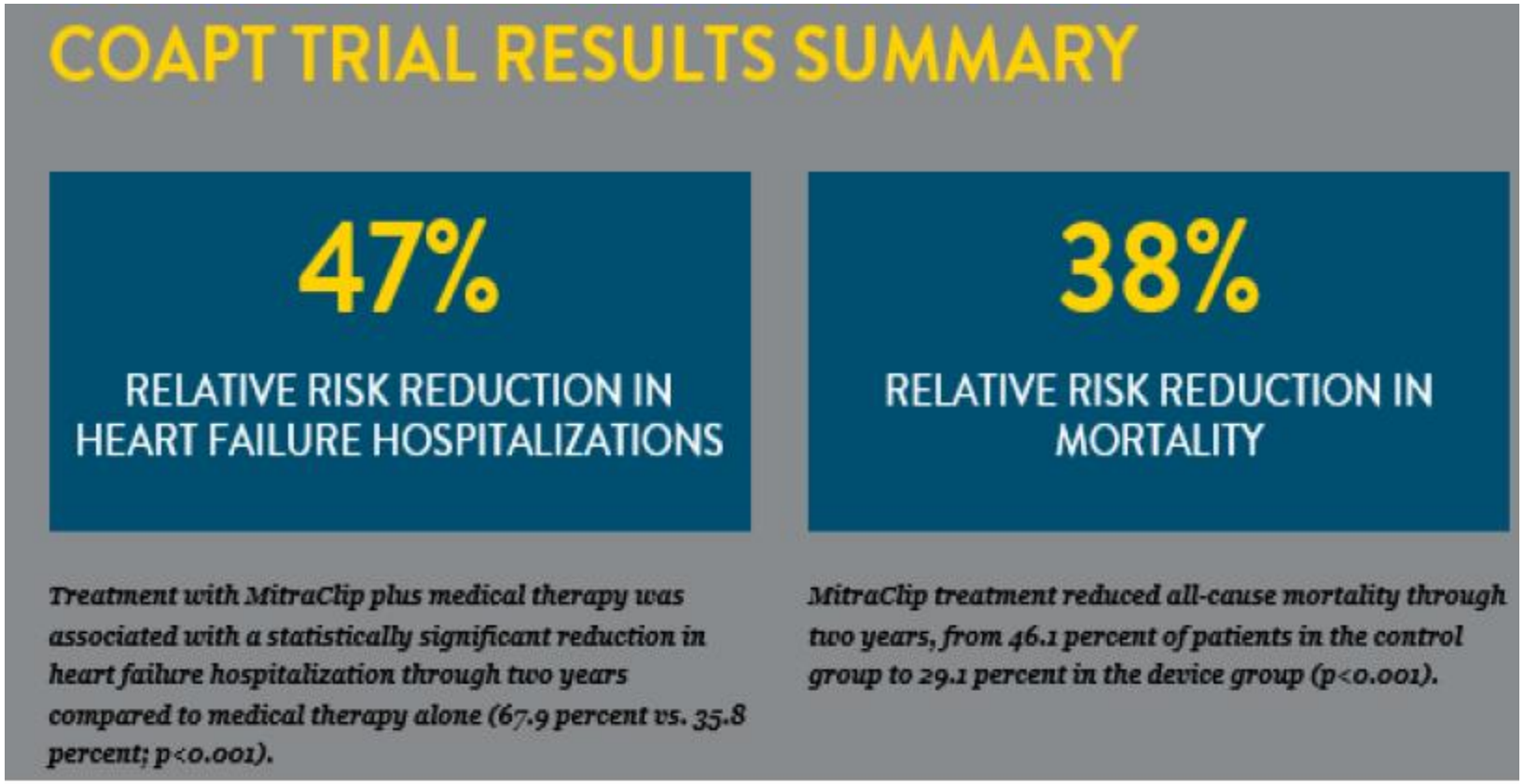
Kaplan-Meier time-to-first event rates

COAPT TRIAL

LVAD or Heart Transplant Within 24 Months



Stone GW et al. NEJM. 2018 Sept 23.



Need to treat 4 patients to prevent 1 HF hospitalization over 2 years

Need to treat 6 patients to prevent 1 Death over 2 years

Why are these 2 RCTs so different ? Possible reasons

		MITRA-FR (n=304)	COAPT (n=614)
Population	**Pre-specified entry criteria** • Severe MR • LVESD	Severe FMR by EU guidelines: EROA >20 mm^2 or RV >30 mL/beat No limits	Severe FMR by US guidelines: EROA >30 mm^2 or RV >45 mL/beat ≤ 70 mm within prior 90 days

Population	**At Baseline**
	• EROA (mean ± SD)
	  • <0.30
	  • 0.30-0.40
	  • >0.40
	• LVEDVi(mean ± SD)
		31 ± 10 mm^2
		52% (157/301)
		32% (95/301)
		16% (49/301)
		135 ± 35 mL/m^2
			41 ± 15 mm^2
			14% (80/591)
			46% (270/591)
			41% (241/591)
			101 ± 34 mL/m^2

Medication	**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

Baseline patient characteristics in the 2 trials

COAPT n≈610

Related to heart failure		
Cause of cardiomyopathy — no. (%)		
Ischemic	184 (60.9)	189 (60.6)
Nonischemic	118 (39.1)	123 (39.4)
NYHA class — no./total no. (%)		
I	1/302 (0.3)	0/311 (0)
II	129/302 (42.7)	110/311 (35.4)
III	154/302 (51.0)	168/311 (54.0)
IVa, ambulatory	18/302 (6.0)	33/311 (10.6)
Hospitalization for heart failure within previous 1 yr — no. (%)	176 (58.3)	175 (56.1)
Previous cardiac resynchronization therapy — no. (%)	115 (38.1)	109 (34.9)
Previous implantation of defibrillator — no. (%)	91 (30.1)	101 (32.4)
B-type natriuretic peptide level — pg/ml	1014.8±1086.0	1017.1±1212.8
N-terminal pro–B-type natriuretic peptide level — pg/ml	5174.3±6566.6	5943.9±8437.6
Assessed at the echocardiographic core laboratory		
Severity of mitral regurgitation — no./total no. (%)		
Moderate-to-severe, grade 3+	148/302 (49.0)	172/311 (55.3)
Severe, grade 4+	154/302 (51.0)	139/311 (44.7)
Effective regurgitant orifice area — cm^2	0.41±0.15	0.40±0.15
Left ventricular end-systolic dimension — cm	5.3±0.9	5.3±0.9
Left ventricular end-diastolic dimension — cm	6.2±0.7	6.2±0.8
Left ventricular end-systolic volume — ml	135.5±56.1	134.3±60.3
Left ventricular end-diastolic volume — ml	194.4±69.2	191.0±72.9
Left ventricular ejection fraction		
Mean — %	31.3±9.1	31.3±9.6
≤40% — no./total no. (%)	231/281 (82.2)	241/294 (82.0)
Right ventricular systolic pressure — mm Hg	44.0±13.4 (253)	44.6±14.0 (275)

100ml/m2

MITRA-FR n≈300

NYHA class — no. (%)		
II	56 (36.8)	44 (28.9)
III	82 (53.9)	96 (63.2)
IV	14 (9.2)	12 (7.9)
Systolic blood pressure — mm Hg	109±16	108±18
Heart rate — beats/min	73±13	72±13
Median EuroSCORE II (IQR)†	6.6 (3.5–11.9)	5.9 (3.4–10.4)
Left ventricular ejection fraction — %	33.3±6.5	32.9±6.7
Left ventricular end-diastolic volume — ml/m^2	136.2±37.4	134.5±33.1
Effective regurgitant orifice area — mm^2	31±10	31±11
Regurgitant volume — ml	45±13	45±14
Median NT-proBNP (IQR) — ng/liter‡	3407 (1948–6790)	3292 (1937–6343)
Median brain natriuretic peptide (IQR) — ng/liter‡	765 (417–1281)	835 (496–1258)
Glomerular filtration rate — ml/min	48.8±19.7	50.2±20.1

MITRA-FR had patients with

- **Larger LVs but Lower Natriuretic Peptides**
- **?? More advanced HF (?? Irreversible)**

Εξέλιξη των ασθενών

COAPT

Table S11. Mitral regurgitation severity at baseline and follow-up in the intention-to-treat population

Echocardiographic core laboratory assessment	Device group	Control group	P value
Baseline	N=302	N=311	
- 3+	148 (49.0%)	172 (55.3%)	0.12
- 4+	154 (51.0%)	139 (44.7%)	
30 days	N=273	N=257	
- 0	2 (0.7%)	2 (0.8%)	
- 1+	197 (72.2%)	19 (7.4%)	
- 2+	54 (19.8%)	67 (26.1%)	<0.001*
- 3+	16 (5.9%)	96 (37.4%)	
- 4+	4 (1.5%)	73 (28.4%)	
- ≤2+	253 (92.7%)	88 (34.2%)	<0.001
- Eligible, not assessed†	n=14	n=40	
6 months	N=240	N=218	
- 0	1 (0.4%)	1 (0.5%)	
- 1+	159 (66.3%)	19 (8.7%)	
- 2+	65 (27.1%)	63 (28.9%)	<0.001*
- 3+	11 (4.6%)	92 (42.2%)	
- 4+	4 (1.7%)	43 (19.7%)	
- ≤2+	225 (93.8%)	83 (38.1%)	<0.001
- Eligible, not assessed†	n=24	n=41	
12 months	N=210	N=175	
- 0	1 (0.5%)	2 (1.1%)	
- 1+	144 (68.6%)	18 (10.3%)	
- 2+	54 (25.7%)	62 (35.4%)	<0.001*
- 3+	9 (4.3%)	60 (34.3%)	
- 4+	2 (1.0%)	33 (18.9%)	
- ≤2+	199 (94.8%)	82 (46.9%)	<0.001
- Eligible, not assessed†	n=24	n=40	
18 months	N=141	N=114	
- 0	1 (0.7%)	1 (0.9%)	
- 1+	105 (74.5%)	13 (11.4%)	
- 2+	28 (19.9%)	32 (28.1%)	<0.001*
- 3+	6 (4.3%)	47 (41.2%)	
- 4+	1 (0.7%)	21 (18.4%)	
- ≤2+	134 (95.0%)	46 (40.4%)	<0.001
- Eligible, not assessed†	n=41	n=38	
24 months	N=114	N=76	
- 0	1 (0.9%)	2 (2.6%)	
- 1+	87 (76.3%)	10 (13.2%)	
- 2+	25 (21.9%)	21 (27.6%)	<0.001*
- 3+	0 (0.0%)	31 (40.8%)	
- 4+	1 (0.9%)	12 (15.8%)	
- ≤2+	113 (99.1%)	33 (43.4%)	<0.001
- Eligible, not assessed†	n=38	n=35	

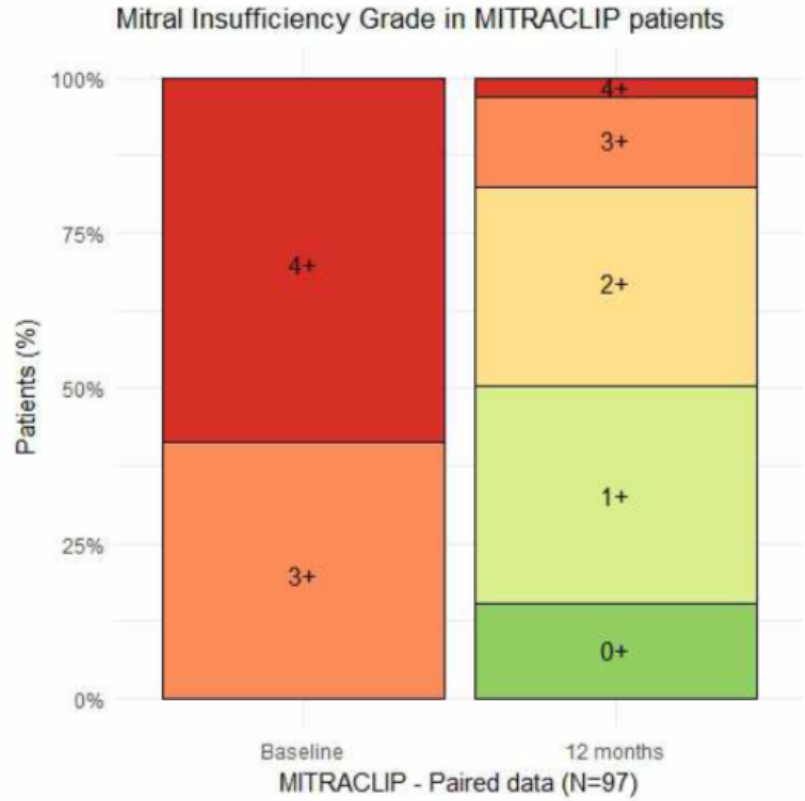
*Proportional odds model for ordinal endpoints. †Patients remaining in the study in whom mitral regurgitation was not assessed.

MR III/IV ~5-6% στους 6 και στους 12 μήνες

MITRA FR

MR III/IV ~15% στους 12 μήνες

X3 vs COAPT



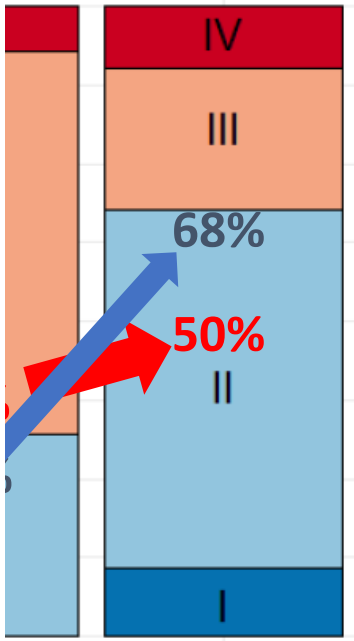
COAPT:
improvement in NYHA I-II
with MC > OMT
from 43 to 72% > from 35 to 50%
Δ 30% vs 15%

MITRA-FR:
improvement in NYHA I-II
with MC similar or < OMT
from 40 to 70% =< from 32 to 68%
Δ 30% vs 36%

Table S17. New York
to-treat population

NYHA class			
Baseline			
- I			
- II			
- III			
- IV			
30 days			
- I			
- II			
- III			
- IV			
- Heart failure death			
- I or II			
- Eligible, not assessed†			
6 months			
- I			
- II			
- III			
- IV			
- Heart failure death			
- I or II			
- Eligible, not assessed†			
12 months			
- I			
- II	55.3% (131/237)	41.8% (97/232)	
- III	17.7% (42/237)	28.0% (65/232)	<0.001*
- IV	2.5% (6/237)	4.7% (11/232)	
- Heart failure death	7.6% (18/237)	17.7% (41/232)	
- I or II	72.2% (171/237)	49.6% (115/232)	<0.001
- Eligible, not assessed†	n=15	n=24	

In both RCTs, MitraClip induced a similar improvement by 30%
But in MitraFR, OMT induced a spectacular improvement ….



PR Group Baseline N=114
PR Group 12 Months N=114
MT Group Baseline N=112
MT Group 12 Months n=112

6 MWdistance; can it get better in these patients already on OMT?

COAPT:

reduction in both arms

Table S15. Change in six-minute walk test distance from baseline to 12 months in the intention-to-treat population

6MWD, meters	Device group	Control group	P value
Baseline, mean ± SD (n)	261.3 ± 125.3 (230)	246.4 ± 127.1 (237)	-
12 months, mean ± SD (n)	256.7 ± 157.7 (230)	188.8 ± 166.7 (237)	-
Change from baseline to 12 months, mean ± SD (n)	-4.6 ± 134.8 (230)	-57.6 ± 152.5 (237)	-
Least square mean change from baseline to 12 months [standard error] (n)	-2.2 [9.1] (230)	-60.0 [9.0] (237)	<0.001*

*Analysis of covariance (ANCOVA) model with baseline score and treatment effect as covariates. 6MWD denotes six-minute walk distance.

MITRA-FR:

improvement in both arms

6-minute walk test distance- m	120	301±126	103	319±127
	82	339±151	77	363±157
6-minute walk variation between baseline and 12-months follow-up	73	25 [-40 ; 71]	57	19 [-27 ; 75]

Changes in Quality of Life – does it getter with time in patients who are already on OMT ?

COAPT

Table S14. Change in Kansas City Cardiomyopathy Questionnaire from baseline to 12 months in the intention-to-treat population

KCCQ Overall Summary Score	Device group	Control group	P value
Baseline, mean ± SD (n)	54.2 ± 22.7 (237)	52.9 ± 23.3 (228)	-
12 months, mean ± SD (n)	66.4 ± 28.6 (237)	49.6 ± 32.0 (228)	-
Change from baseline to 12 months, mean ± SD (n)	12.2 ± 30.3 (237)	-3.2 ± 30.0 (228)	-
Least square mean change from baseline to 12 months [standard error] (n)	12.5 [1.8] (237)	-3.6 [1.9] (228)	<0.001*

*Analysis of covariance (ANCOVA) model with baseline score and treatment effect as covariates. KCCQ denotes Kansas City Cardiomyopathy Questionnaire.

MITRA FR

Quality of life (global score)[f]				
Baseline	143	51.5±19.2	128	53.2±16.6
12 months	93	60.8±20.3	87	58.6±18.2

Medical treatment at baseline

COAPT

Medications at baseline		N=302	N=312	
Beta-blocker	**89%**	91.1% (275/302)	89.7% (280/312)	0.58
ACEI, ARB or ARNI	**84%**	71.5% (216/302)	62.8% (196/312)	0.02
- ACEI		45.7% (138/302)	36.9% (115/312)	0.03
- ARB		21.9% (66/302)	23.1% (72/312)	0.72
- ARNI		4.3% (13/302)	2.9% (9/312)	0.34
Mineralocorticoid receptor antagonist	**55%**	50.7% (153/302)	49.7% (155/312)	0.81
Nitrate		6.3% (19/302)	8.0% (25/312)	0.41
Hydralazine		16.6% (50/302)	17.6% (55/312)	0.72
Nitrate plus hydralazine		5.0% (15/302)	5.8% (18/312)	0.66
Diuretic	**99%**	89.4% (270/302)	88.8% (277/312)	0.80
Chronic oral anticoagulant, any		46.4% (140/302)	40.1% (125/312)	0.12
- Warfarin		31.1% (94/302)	28.2% (88/312)	0.43
- Direct acting oral anticoagulant		15.2% (46/302)	12.2% (38/312)	0.27
Aspirin		57.6% (174/302)	64.7% (202/312)	0.07
P2Y12 receptor inhibitor, any		25.2% (76/302)	22.8% (71/312)	0.48
- Clopidogrel		21.5% (65/302)	20.5% (64/312)	0.76
- Prasugrel		2.6% (8/302)	0.6% (2/312)	0.06
- Ticagrelor		1.0% (3/302)	1.9% (6/312)	0.51
- Prasugrel or ticagrelor		3.6% (11/302)	2.6% (8/312)	0.44
Statin		62.6% (189/302)	60.6% (189/312)	0.61

- ICD 30 - 32%
- CRT 38 - 35%

MITRA-FR

ACEi/ARB	111/152 (73.0)	113/152 (74.3)
Angiotensin receptor and neprilysin inhibitors	14/140 (10.0)	17/140 (12.1)
Beta-blockers	134/152 (88.2)	138/152 (90.8)
Mineralocorticoid receptor antagonists	86/152 (56.6)	80/151 (53.0)
Loop Diuretics	151/152 (99.3)	149/152 (98.0)
Oral anticoagulants	93/152 (61.2)	93/152 (61.2)

- ICD 32 - 38%
- CRT 31 - 23%

Baseline medical tx looks similar (or even better in Mitra-FR) but

- no data on the doses
- MITRA-FR gives no data on meds changes at f-up; changes should not be great !

Medical tx should have been maximal from baseline

COAPT

Table S7. Major changes in heart failure medications during the first 12 months of follow-up

Medication	Device group (n=302)	Control group (n=312)	P value
ACEI, ARB or ARNI			
- Decrease dose by >50% or discontinue	6.6% (20/302)	4.8% (15/312)	0.33
- Increase dose by >100% or new drug class started	7.6% (23/302)	7.4% (23/312)	0.91
Beta-blocker			
- Decrease dose by >50% or discontinue	5.3% (16/302)	5.1% (16/312)	0.92
- Increase dose by >100% or new drug class started	8.6% (26/302)	3.8% (12/312)	0.01
Mineralocorticoid receptor antagonist			
- Decrease dose by >50% or discontinue	0.7% (2/302)	0.6% (2/312)	1.00
- Increase dose by >100% or new drug class started	5.3% (16/302)	2.6% (8/312)	0.08
Nitrates			
- Decrease dose by >50% or discontinue	0.0% (0/302)	0.0% (0/312)	1.00
- Increase dose by >100% or new drug class started	1.0% (3/302)	1.9% (6/312)	0.51
Hydralazine			
- Decrease dose by >50% or discontinue	1.0% (3/302)	0.0% (0/312)	0.12
- Increase dose by >100% or new drug class started	4.3% (13/302)	3.8% (12/312)	0.77

MITRA-FR

NOT AVAILABLE

In COAPT, the MitraClip therapy allowed greater doses of RAASi and BBs

- Better BP and HR
- Better clinical status

MitraClip procedure - complications

Generally thought to be a low-complication procedure (with a long learning curve)

- Operators can take their time during the procedure to achieve a result as good as possible
- Right side of the circulation

COAPT

- **2% device implantation failure**
- **3.4% complications at 12 months**

MITRA-FR

- **4% device implantation failure**
- **14.6% peri-procedural complications**

Why are these 2 RCTs so different ? Possible reasons

	MITRA-FR (n=304)	COAPT (n=614)
Central Eligibility Committee	None	Yes
Primary Effectiveness	All-cause death and unplanned HF hospitalization through 12 months (1st event)	Recurrent HF hospitalizations through 24 months, analyzed when last pt finishes 12 months (all events)
Pre-specified powered secondary endpoints	None	10 powered endpoints
Acute results: No clip / ≥3+ MR	9% / 9%	5% / 5%
Procedural complications*	14.6%	8.5%
12-mo MitraClip™ ≥3+ MR	17%	5%

Less well trained operators

In both RCTs, MitraClip induced an improvement in MR, functional status, 6MWT and QOL
In Mitra-FR, OMT did better !!!

Less well treated patients at baseline

I don’t like (at all) the Abbott analysis trying to identifying benefit

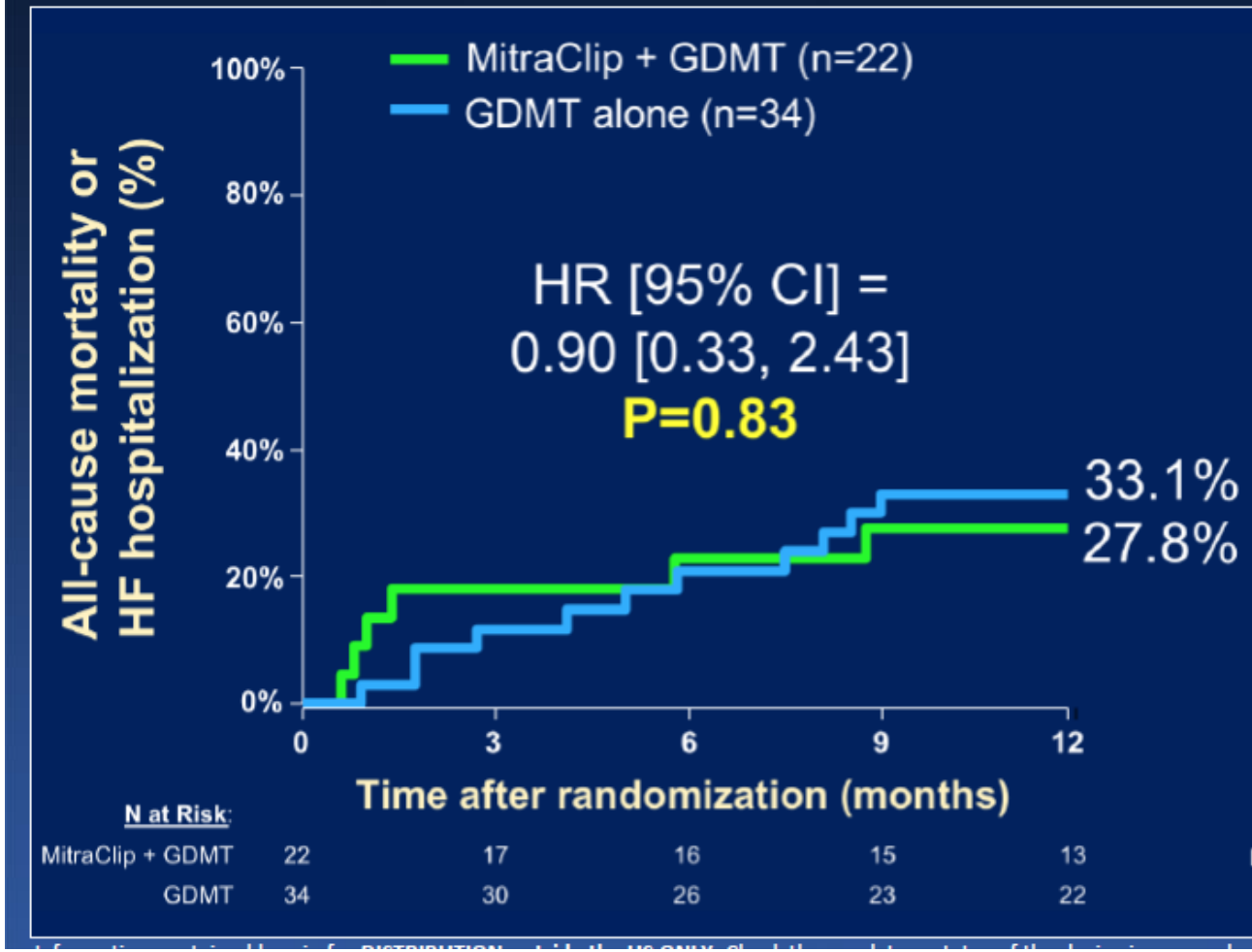
in specific groups based on EROA

COAPT TRIAL

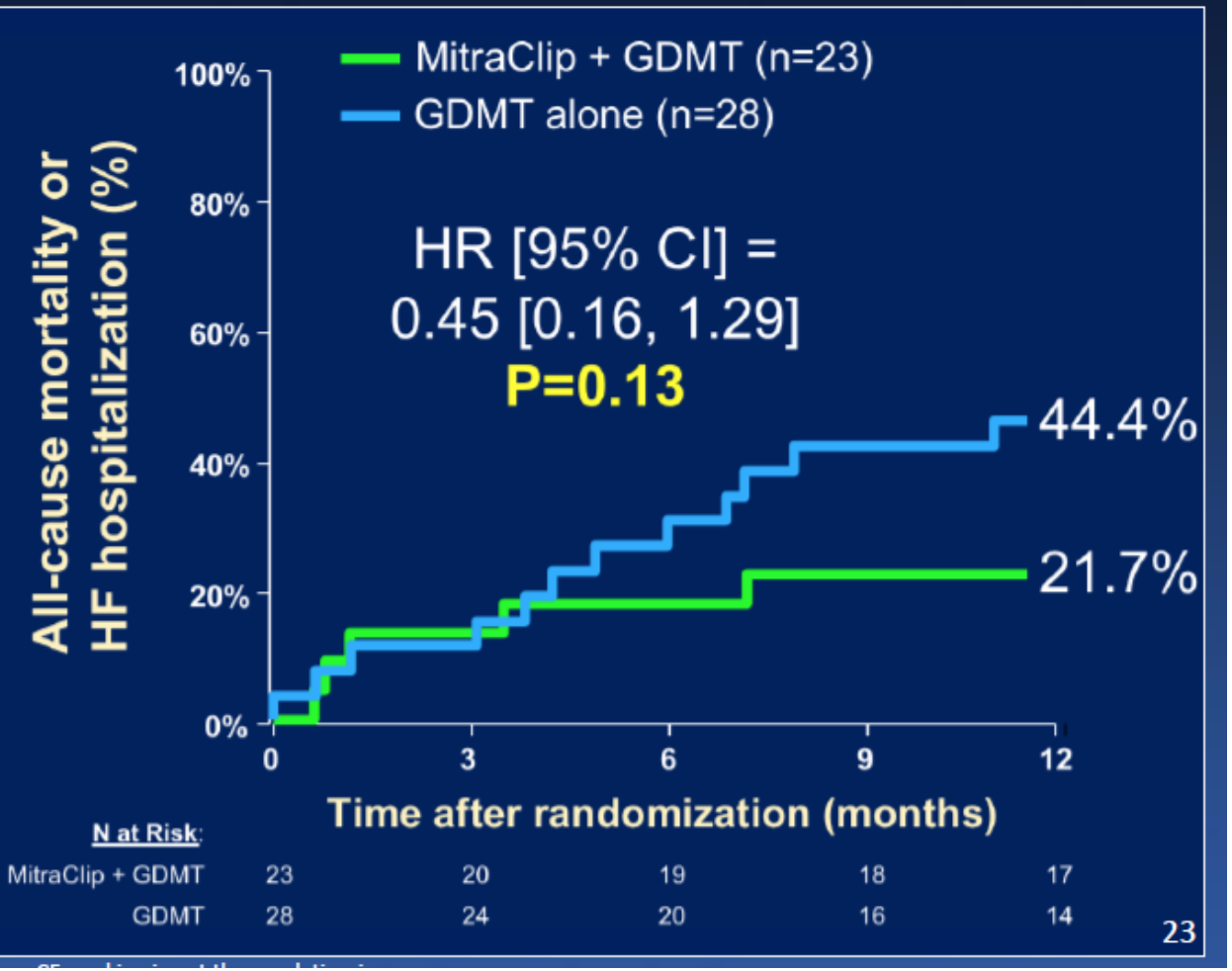
Impact of EROA and LVEDV: EROA ≤30 mm²

All-cause mortality or HF hospitalization through 12 months

LVEDVI >96 ml/m² (N=56; 10.2%)



LVEDVI ≤96 ml/m² (N=51; 9.3%)

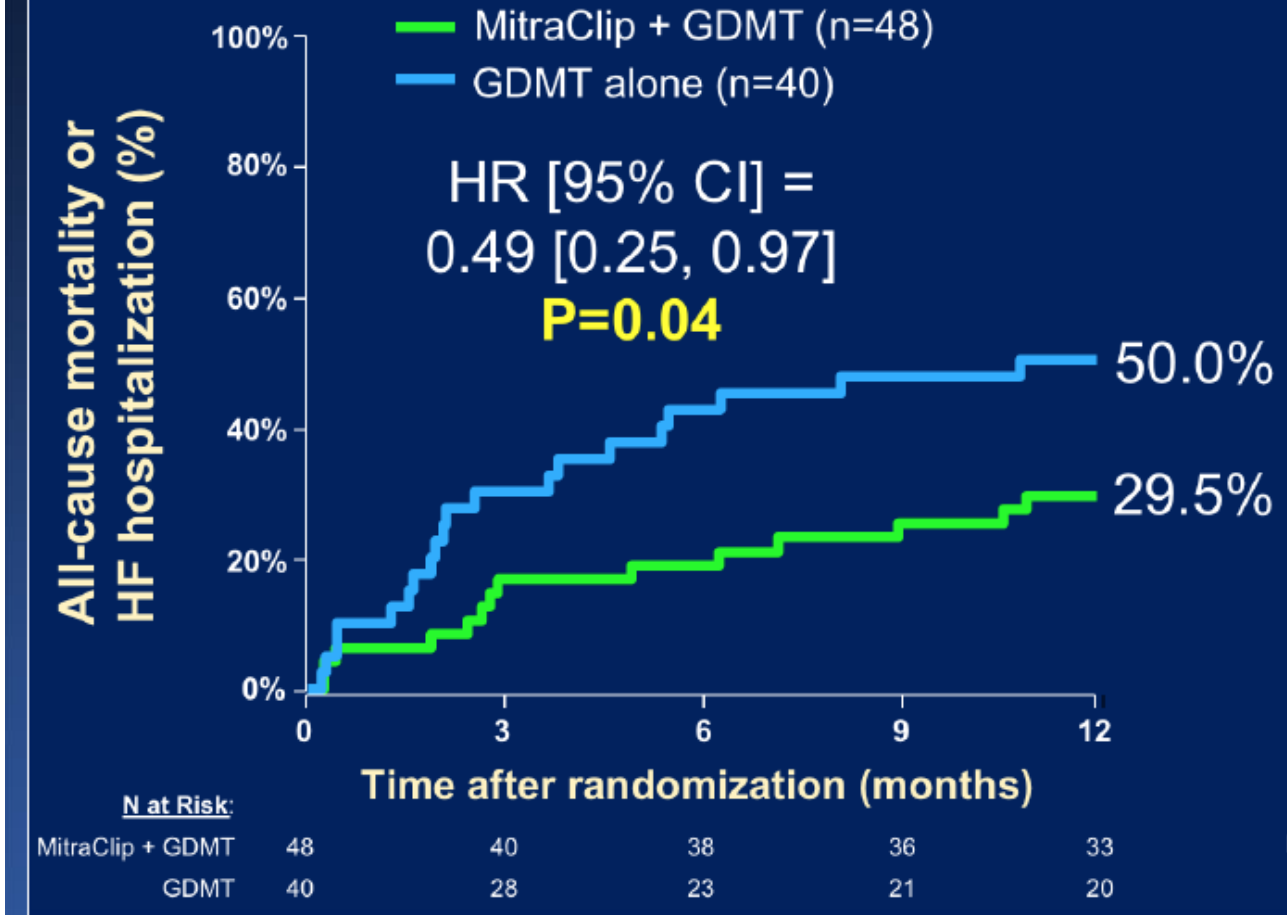


COAPT TRIAL

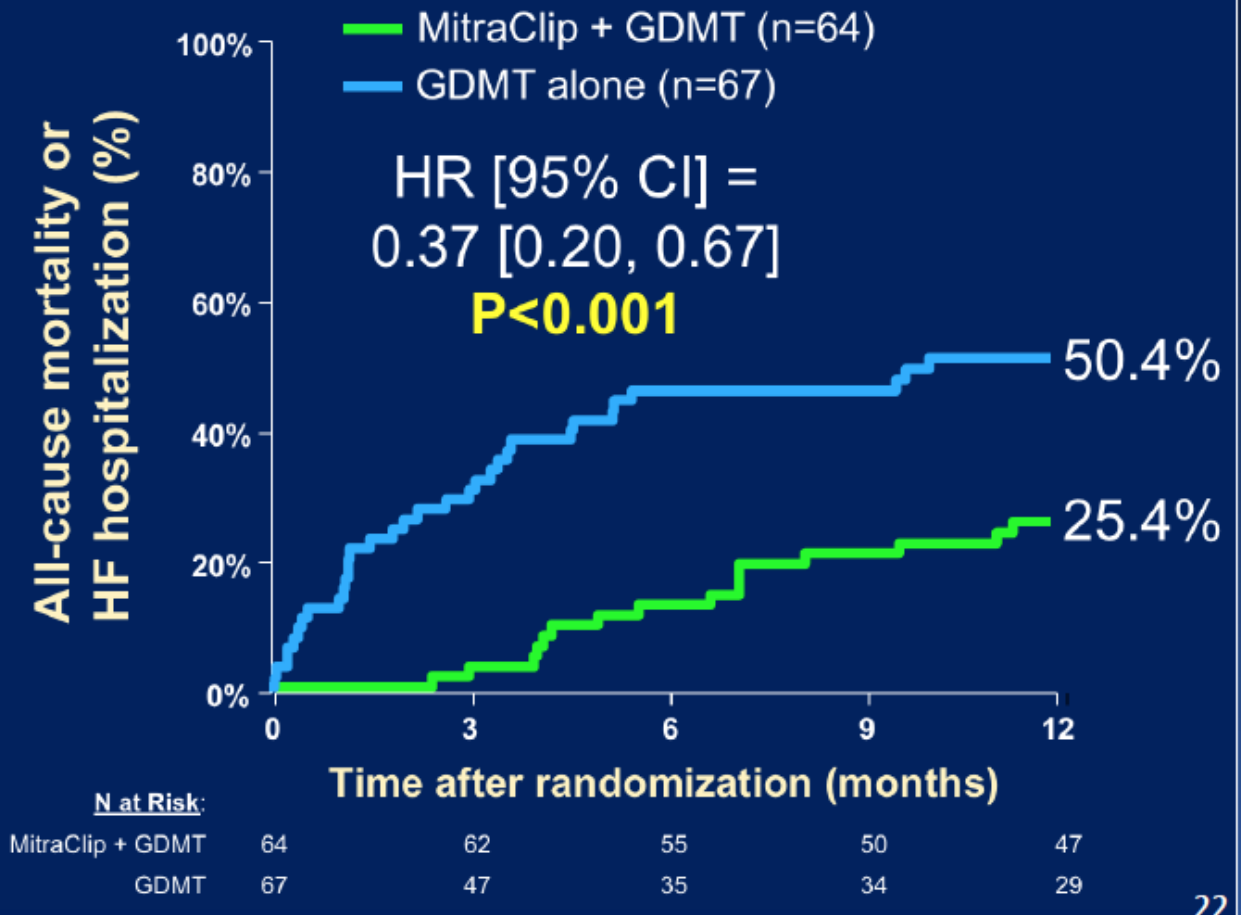
Impact of EROA and LVEDV: EROA >30-40 mm²

All-cause mortality or HF hospitalization through 12 months

LVEDVI >96 ml/m² (N=88; 16.1%)



LVEDVI ≤96 ml/m² (N=131; 23.9%)



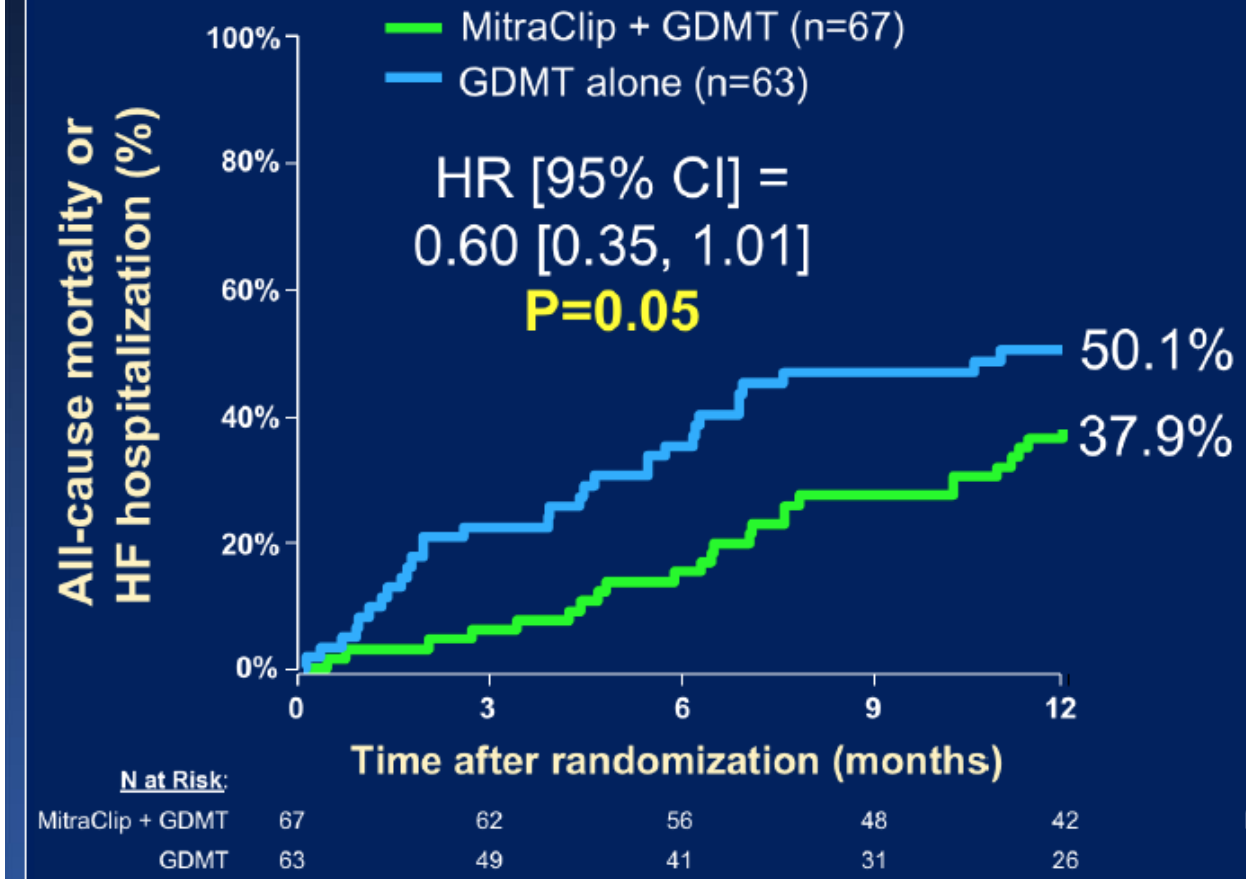
COAPT TRIAL

Impact of EROA and LVEDV

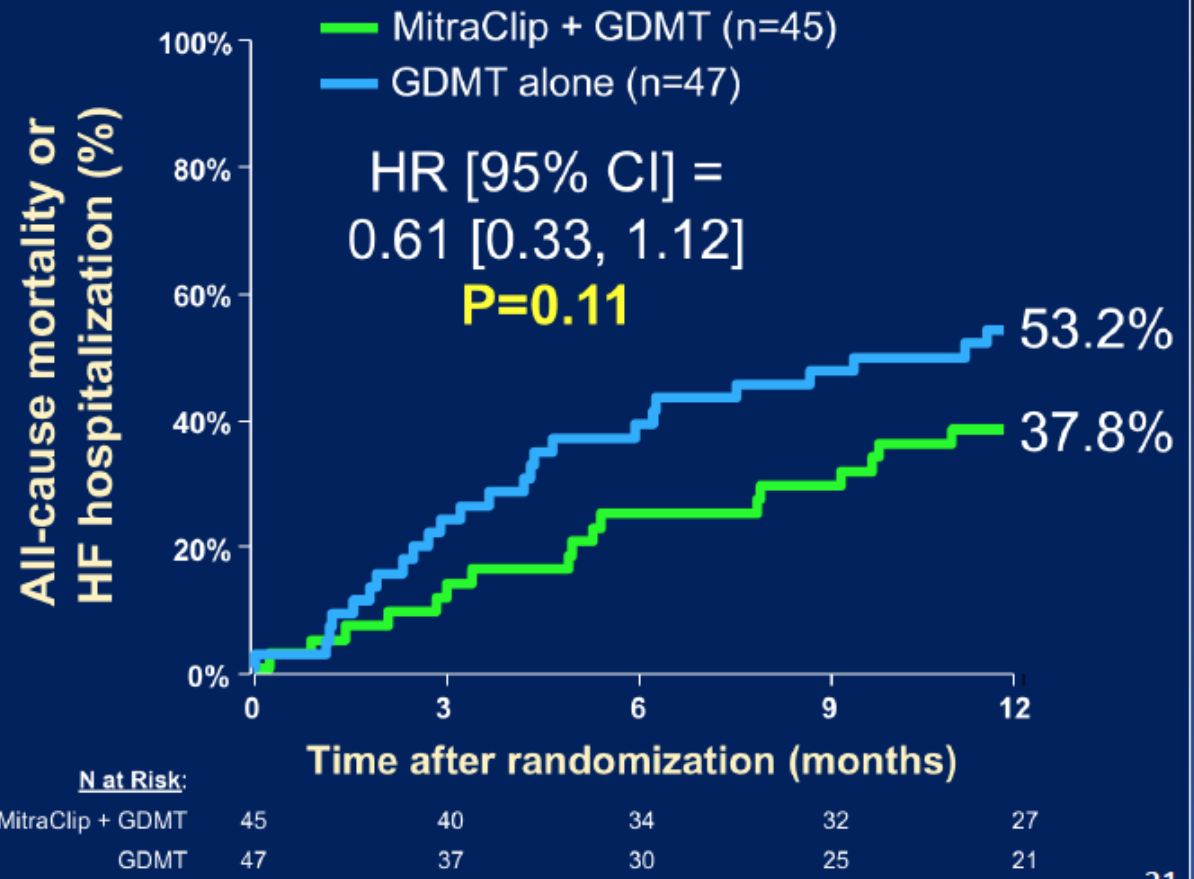
EROA >40 mm²

All-cause mortality or HF hospitalization through 12 months

LVEDVI >96 ml/m² (N=130; 23.7%)



LVEDVI ≤96 ml/m² (N=92; 16.8%)



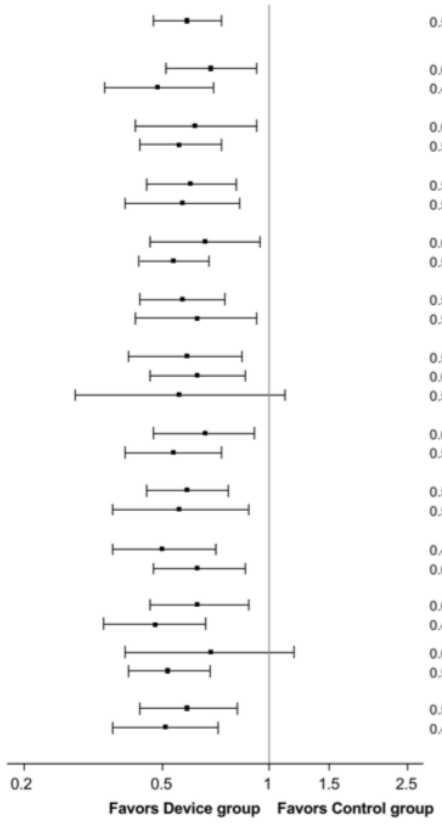
I don’t like and I don’t believe the Abbott analysis trying to identifying benefit in specific groups based on EROA (small numbers)

- MR is a very dynamic phenomenon (BP, diuresis, HR…)
- MR is notoriously difficult to quantify (2D, 3D, PISA, whatever method)
- MR assessment is comphrehensive
- MR assessment is done by eye-balling characteristics by many famous echocardiographers

Subgroup analysis

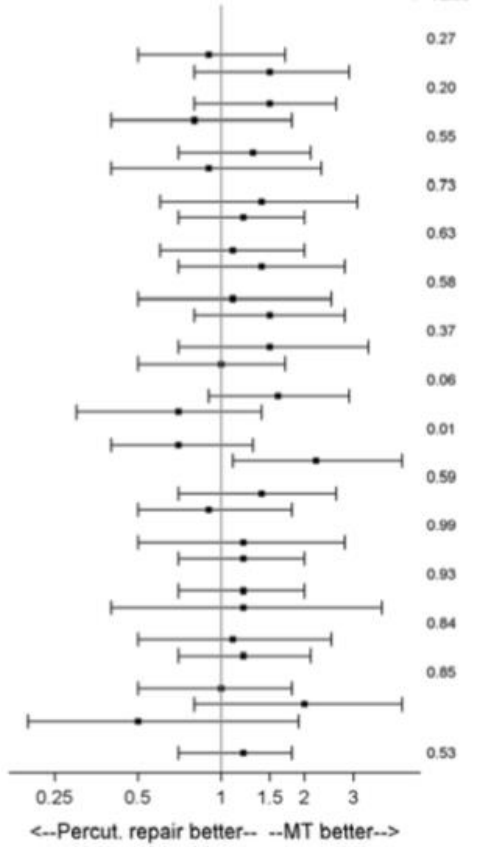
COAPT: benefit in all

Subgroup	Device group	Control Group	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 [0.40, 0.71]	
Heart failure 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 mitral regurgitation 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 left ventricular ejection fraction				
≥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 left ventricular end-diastolic volume (median)				
≥181 mL (n=288)	48.9% (64)	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]	



MITRA-FR: benefit in none

Subgroup	Percut. repair Events/N (%)		Medical treatment Events/N (%)		OR (95% CI)	P Value*
CENTRE SIZE						0.27
N <= 15 Randomized patients	33/73	(45.2)	35/73	(47.9)	0.90 (0.50, 1.70)	
N > 15 Randomized patients	50/77	(64.9)	43/78	(55.1)	1.50 (0.80, 2.90)	
AGE						0.20
<= 75 Yr	52/100	(52.0)	39/93	(41.9)	1.50 (0.80, 2.60)	
> 75 Yr	31/50	(62.0)	39/58	(67.2)	0.80 (0.40, 1.80)	
GENDER						0.55
Male	67/120	(55.8)	53/106	(50.0)	1.30 (0.70, 2.10)	
Female	16/30	(53.3)	25/45	(55.6)	0.90 (0.40, 2.30)	
NYHA						0.73
Class II	26/56	(46.4)	17/44	(38.6)	1.40 (0.60, 3.10)	
Class III/IV	57/94	(60.6)	61/107	(57.0)	1.20 (0.70, 2.00)	
ISCHEMIC CARDIOMYOPATHY						0.63
Yes	49/94	(52.1)	42/84	(50.0)	1.10 (0.60, 2.00)	
No	34/56	(60.7)	35/66	(53.0)	1.40 (0.70, 2.80)	
PULMONARY ARTERY PRESSURE						0.58
< 50 mmHg	23/53	(43.4)	18/44	(40.9)	1.10 (0.50, 2.50)	
≥ 50 mmHg	49/73	(67.1)	51/88	(58.0)	1.50 (0.80, 2.80)	
ATRIAL FIBRILLATION						0.37
Yes	30/49	(61.2)	24/47	(51.1)	1.50 (0.70, 3.40)	
No	46/91	(50.5)	51/99	(51.5)	1.00 (0.50, 1.70)	
PREVIOUS HOSPIT FOR CHF						0.06
< 2	53/95	(55.8)	38/87	(43.7)	1.60 (0.90, 2.90)	
≥ 2	30/55	(54.5)	40/62	(64.5)	0.70 (0.30, 1.40)	
CREATININE						0.01
< 1 5 mg/dl	31/75	(41.3)	43/85	(50.6)	0.70 (0.40, 1.30)	
≥ 1 5 mg/dl	51/72	(70.8)	34/65	(52.3)	2.20 (1.10, 4.50)	
HEMOGLOBINE						0.59
< Median	43/75	(57.3)	33/65	(50.8)	1.40 (0.70, 2.60)	
≥ 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



COAPT is a landmark trial

- In patients with HF and moderate-to-severe or severe secondary MR who remain symptomatic despite maximally-tolerated GDMT, transcatheter mitral leaflet approximation with the MitraClip, during 24-month follow up, was:
  - safe
  - provided durable reduction in MR
  - reduced the rate of HF hospitalizations, and
  - improved survival, quality-of-life and functional capacity
- 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

Conclusions

Changes in Clinical Practice Anticipated

COAPT is for MitraClip in MR
similar to
PARTNERS was for TAVI in AS

tctMD/the heart beat News Conferences Slides & More

NEWS • INTERVENTIONAL

FDA Extends MitraClip Indication to Include Functional MR

The expanded approval, based on COAPT, means that a far larger proportion of mitral regurgitation patients will be eligible for percutaneous repair.

By Shelley Wood | March 14, 2019

Σας ευχαριστώ πολύ

για την προσοχή

Ιατρείο ΚΑ ΠΓΝΙ - 2651099847
heartfailure.uhi@gmail.com
https://bcardio.gr/index.php/el/

Σας ευχαριστώ
για την προσοχή σας

University Campus &
University Hospital, Ioannina