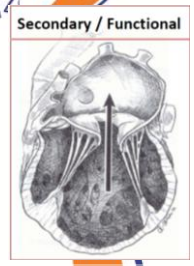
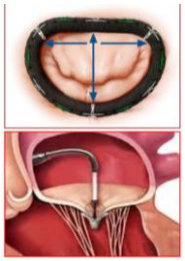




Krajská zdravotní, a.s.
- Masarykova nemocnice v Ústí nad Labem, o.z.

COAPT TRIAL

The COAPT Trial

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

P. Červinka
Klinika kardiologie, Masarykova nemocnice v Ústí n.L., o.z.,
Krajská zdravotní, a.s. a UJEP v Ústí n. L.

(XXVII. Sjezd ČKS, Brno 12.-15.5. 2019)

Krajská zdravotní, a.s.
- Masarykova nemocnice v Ústí nad Labem, o.z.

„BACKGROUND 1“

- Nemocní se srdečním selháním (SS), u kterých vznikne mitrální regurgitace (MR) sekundárně k dysfunkci komory, mají špatnou prognózu, horší QoL, častější hospitalizace pro SS a snížené přežívání

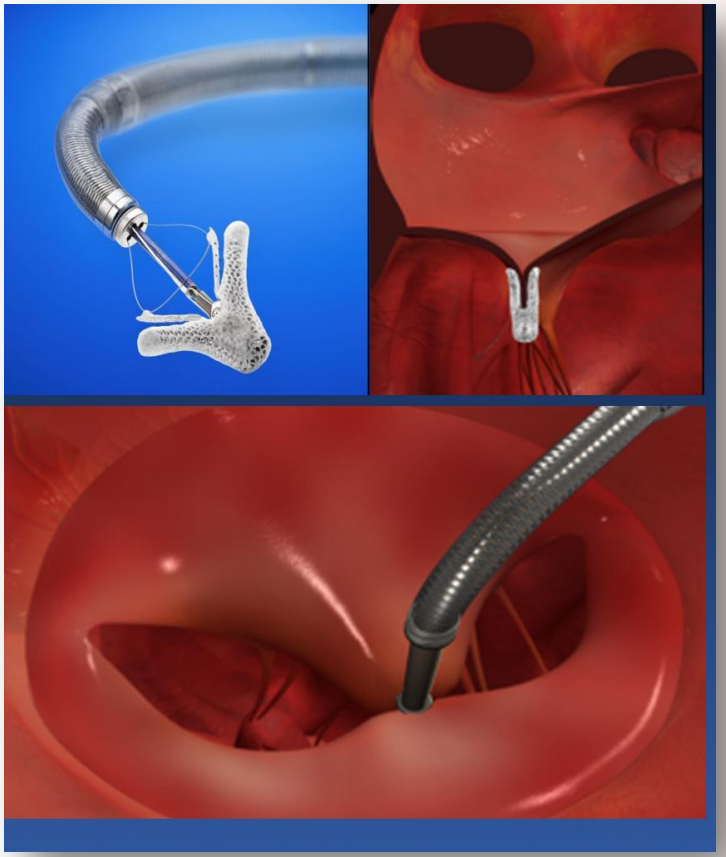
- Není žádná účinná léčba sekundární MR u SS
  - GDMT (doporučeními-vedená konzervativní léčba) a srdeční resynchronizace (CRT) může zlepšit symptomy u některých nemocných

- Zda korekce sekundární MR zlepší prognózu nemocných se SS není známo
  - Chirugický zákrok/anuloplastika/ neprokázala efektivitu a má vysoký výskyt rekurence MR

COAPT TRIAL

„BACKGROUND 2“

- MitraClip redukuje MR přiblížením předního a zadního cípu a vytvořením „double-oriffice“
- Data z registrů prokázala, že výkon je bezpečný a redukuje symptomy u nemocných se SS a sekundární MR
- COAPT je randomizovaná studie hodnotící bezpečnost a účinnost MitraClipu u nemocných se SS a sekundární MR, kteří jsou symptomatičtí navzdory GDMT



COAPT TRIAL

ZAŘAZOVACÍ KRITÉRIA

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

COAPT TRIAL

VYLUČUJÍCÍ KRITÉRIA

1. ACC/AHA stage D HF, hemodynamic instability or cardiogenic shock
2. Untreated clinically significant CAD requiring revascularization
3. COPD requiring continuous home oxygen or chronic oral steroid use
4. Severe pulmonary hypertension or moderate or severe right ventricular dysfunction
5. Aortic or tricuspid valve disease requiring surgery or transcatheter intervention
6. Mitral valve orifice area <4.0 cm^2 by site-assessed TTE
7. Life expectancy <12 months due to non-cardiac conditions

COAPT TRIAL

CENTRÁLNÍ ECHO LAB, „PŘEZKUMOVÁ KOMISE“

1. A Central Echo Core Lab confirmed the presence of 3+ - 4+ secondary MR
2. Potentially eligible pts were then presented by the local site investigators on weekly calls to a Central Eligibility Committee consisting of at a minimum a heart failure specialist and expert mitral valve surgeon
3. The CEC confirmed that all eligibility criteria were met, especially 1) use of maximally-tolerated GDMT for heart failure, and treatment with CRT, defibrillators and revascularization if appropriate, and that 2) mitral valve surgery was not considered appropriate at the treating center and would not be offered to the patient, even if randomized to control
4. Pts not meeting these criteria were rejected, or in some cases were deferred and could be re-presented after suitable GDMT had been instituted if the pt remained symptomatic and repeat echo still showed 3+-4+ MR

PRIMÁRNÍ SLEDOVANÉ CÍLE

Sample Size and Power Analysis

Primary Effectiveness Endpoint

Analyzed using a joint frailty model to account for the competing risk of death

Assumptions

Annualized HF hosp rates: 0.60 per pt-yr Control vs. 0.42 per pt-yr Device

12-month mortality rates: 27% Control vs. 22% Device

12-month attrition rate: 7.5%

Power

610 randomized pts provided 80% power at a 1-sided α of 0.05 to demonstrate superiority of the Device group compared with the Control group for the 24-month rate of all HF hospitalizations

Primary Safety Endpoint

305 pts in the Device group provided >95% power to demonstrate that freedom from device-related complications at 12 months is more than a pre-specified objective performance goal of 88% at a one-sided α of 0.05

COAPT TRIAL

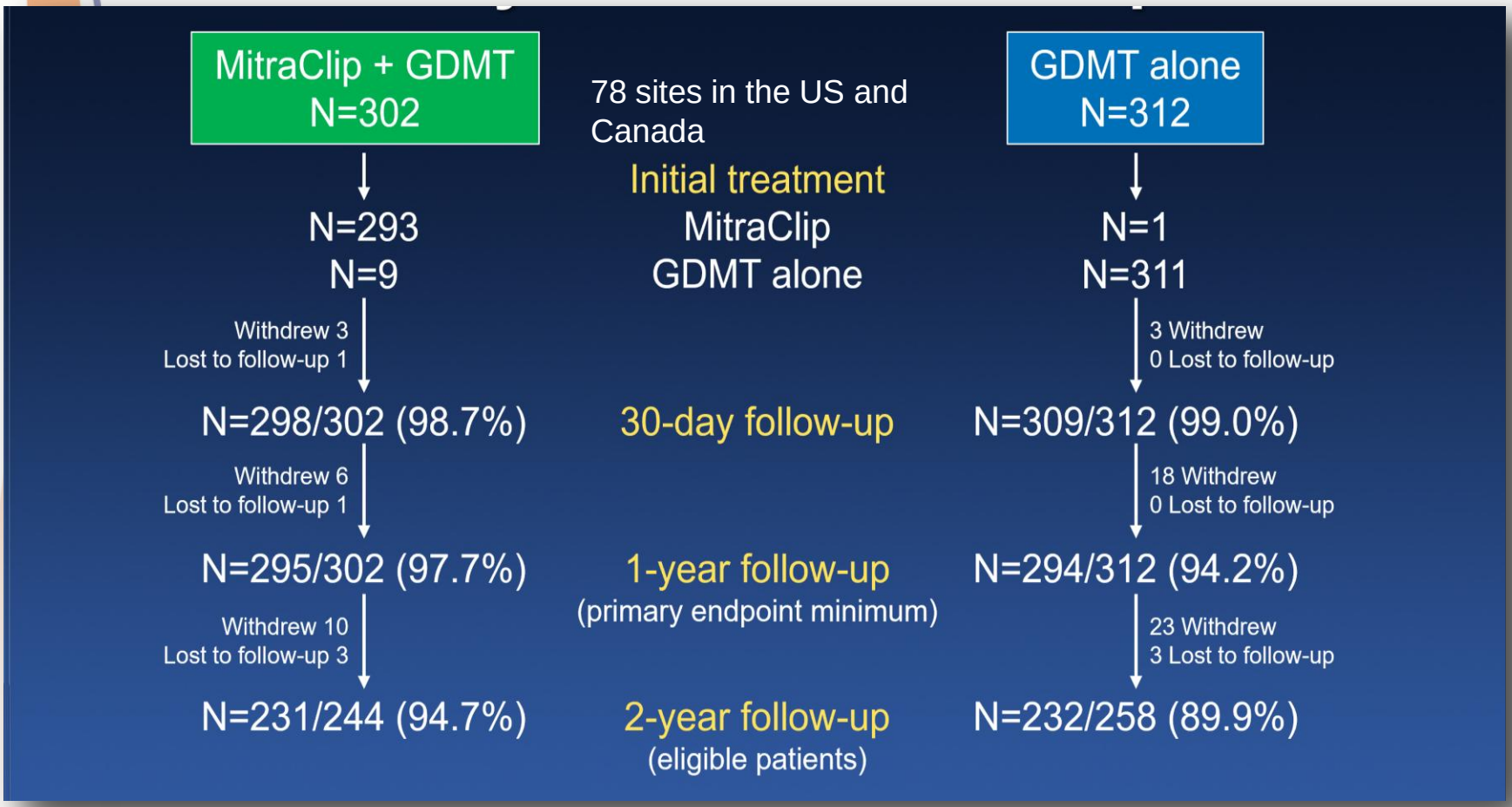
SEKUNDÁRNÍ SLEDOVANÉ CÍLE

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

PRŮBĚH STUDIE A SLEDOVÁNÍ



COAPT TRIAL

ZÁKLADNÍ CHARAKTERISTIKY

HF parameters	MitraClip + GDMT (N=302)	GDMT alone (N=312)
Etiology of HF		
- Ischemic	60.9%	60.6%
- Non-ischemic	39.1%	39.4%
NYHA class		
- I	0.3%	0%
- II	42.7%	35.4%
- III	51.0%	54.0%
- IV	6.0%	10.6%
HF hosp w/i 1 year	58.3%	56.1%
Prior CRT	38.1%	34.9%
Prior defibrillator	30.1%	32.4%

Echo core lab	MitraClip + GDMT (N=302)	GDMT alone (N=312)
MR severity		
- Mod-to-sev (3+)	49.0%	55.3%
- Severe (4+)	51.0%	44.7%
EROA, cm^2	0.41 ± 0.15	0.40 ± 0.15
LVESD, cm	5.3 ± 0.9	5.3 ± 0.9
LVEDD, cm	6.2 ± 0.7	6.2 ± 0.8
LVESV, mL	135.5 ± 56.1	134.3 ± 60.3
LVEDV, mL	194.4 ± 69.2	191.0 ± 72.9
LVEF, %	31.3 ± 9.1	31.3 ± 9.6
- ≤40%	82.2%	82.0%
RVSP, mmHg	44.0 ± 13.4	44.6 ± 14.0

COAPT TRIAL

MEDIKACE

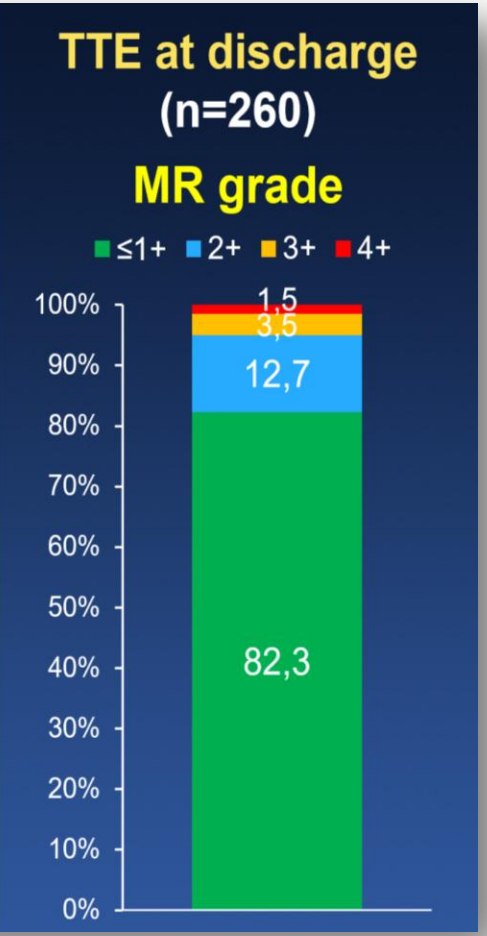
Major Changes in HF Meds w/i 12 Months

	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

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

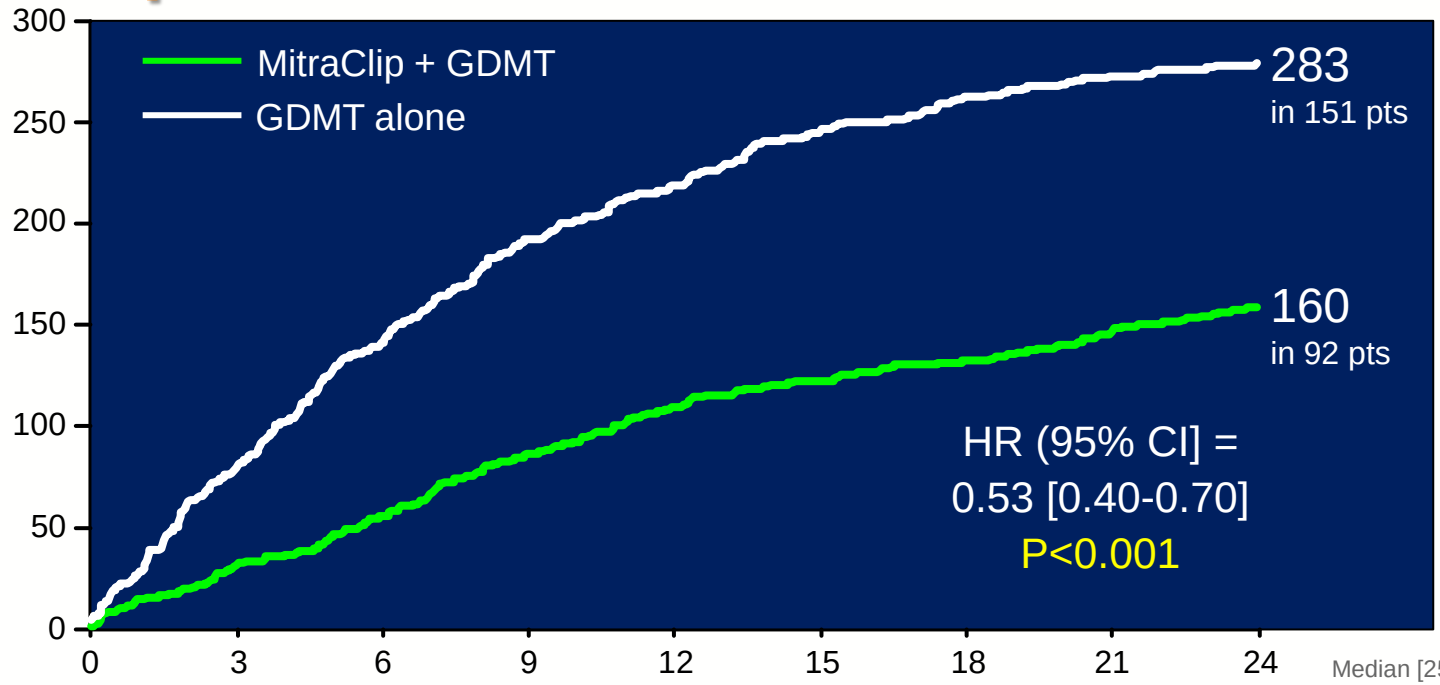


COAPT TRIAL

VÝSLEDKY

Primary Effectiveness Endpoint

All Hospitalizations for HF within 24 months



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

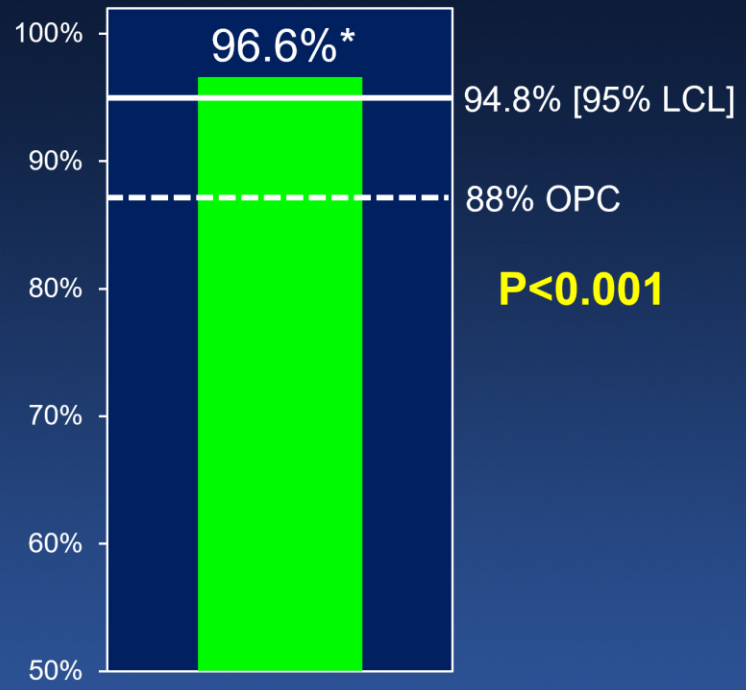
No. at Risk:									
MitraClip	302	286	269	253	236	191	178	161	124
GDMT	312	294	271	245	219	176	145	121	88

- **NNT to prevent 1 hospitalization for heart failure within 24 months was 3.1 (95% CI, 1.9 to 7.9).**

VÝSLEDKY

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%

VÝSLEDKY

Powered Secondary Endpoints

- Tested in hierarchical order[1] -

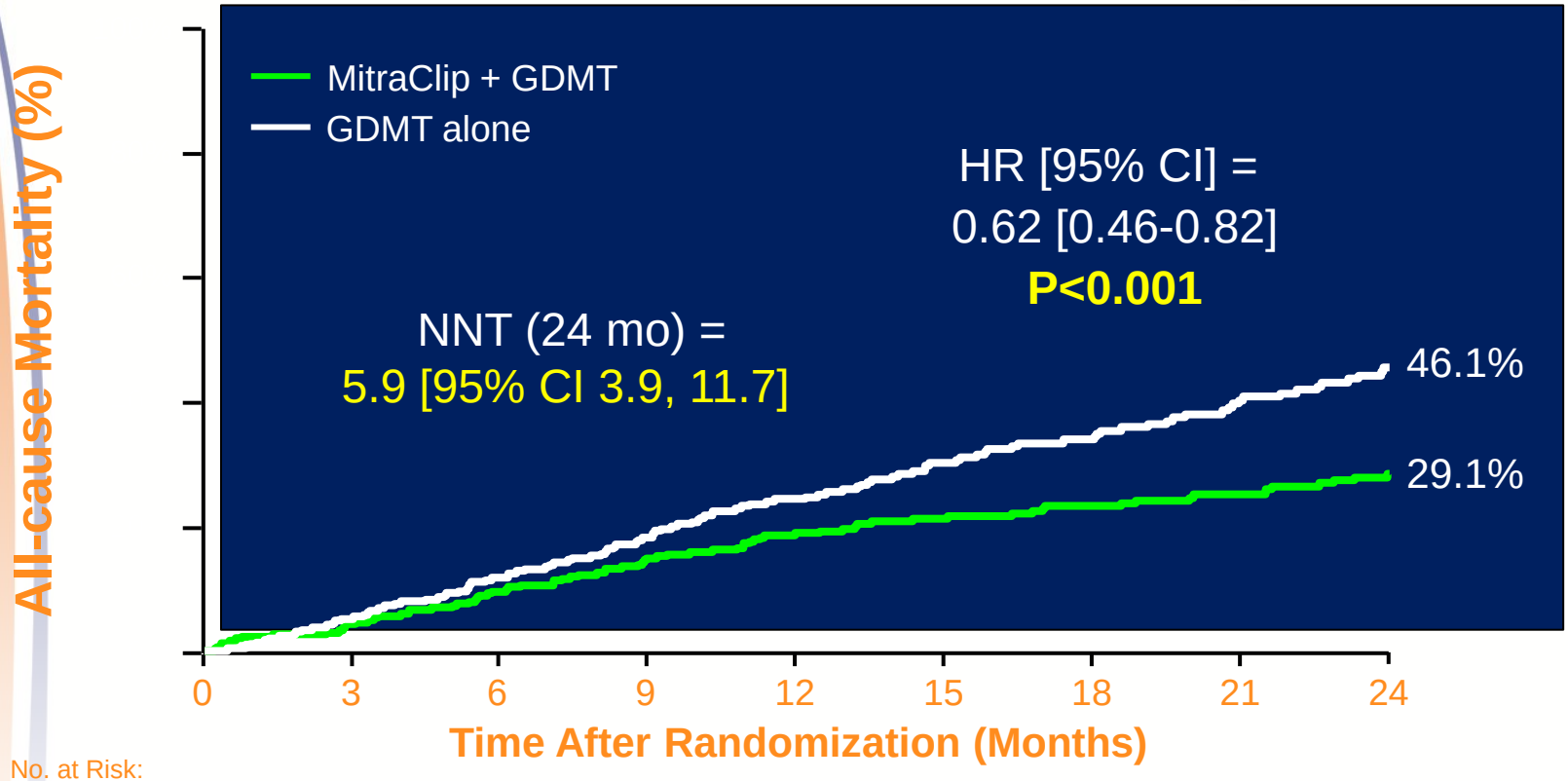
	P-value
1. MR grade ≤2+ at 12 months	<0.001
2. All-cause mortality at 12 months[2]	<0.001
3. Death and all HF hospitalization through 24 months (Finkelstein-Schoenfeld)	<0.001
4. Change in QOL (KCCQ) from baseline to 12 months	<0.001
5. Change in 6MWD from baseline to 12 months	<0.001
6. All-cause hospitalizations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

VÝSLEDKY

All-cause Mortality

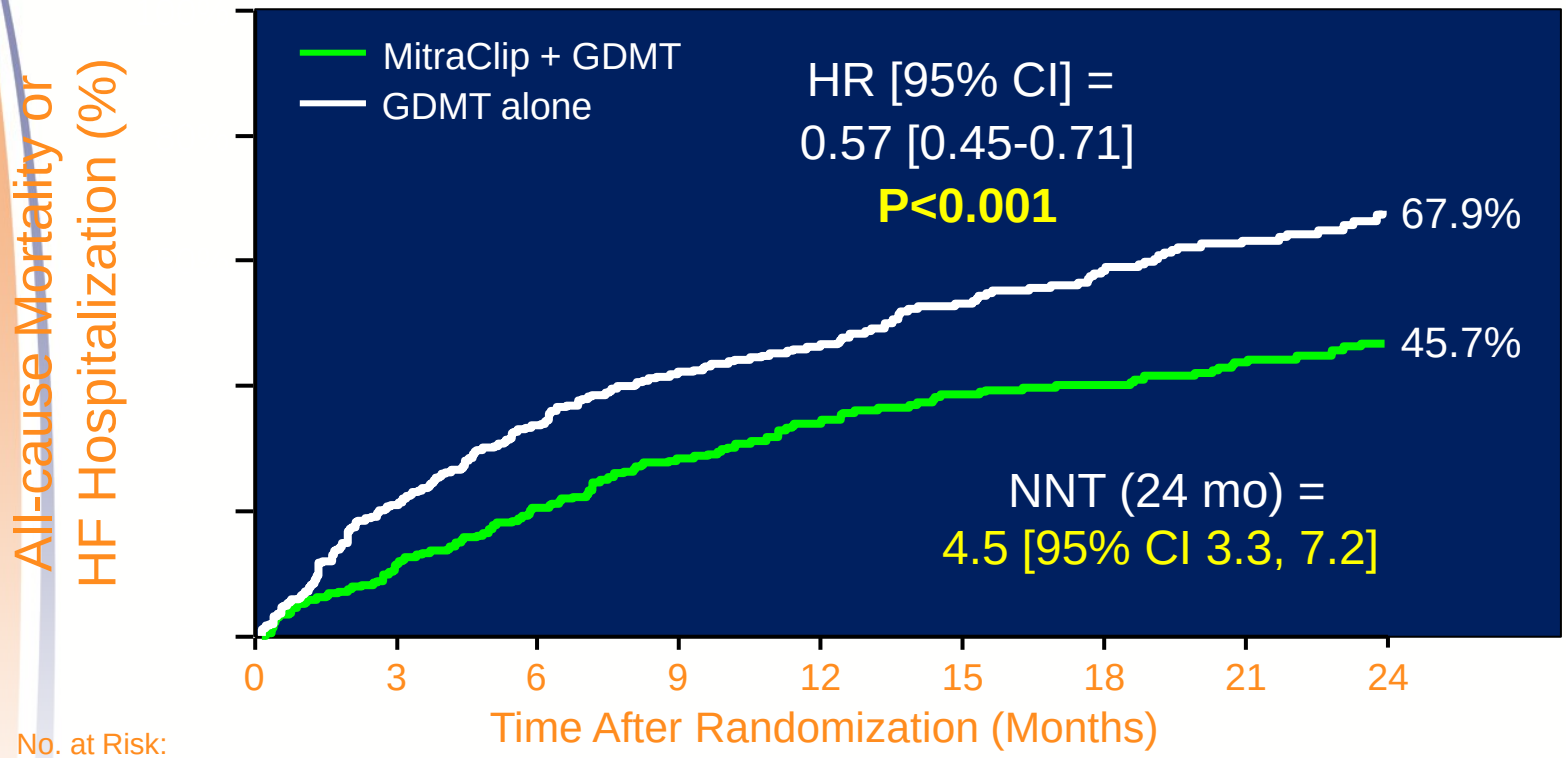


No. at Risk:									
MitraClip + GDMT	302	286	269	253	236	191	178	161	124
GDMT alone	312	294	271	245	219	176	145	121	88

COAPT TRIAL

VÝSLEDKY

Death or HF Hospitalization



No. at Risk:									
MitraClip + GDMT	302	264	238	215	194	154	145	126	97
GDMT alone	312	244	205	174	153	117	90	75	55

COAPT TRIAL

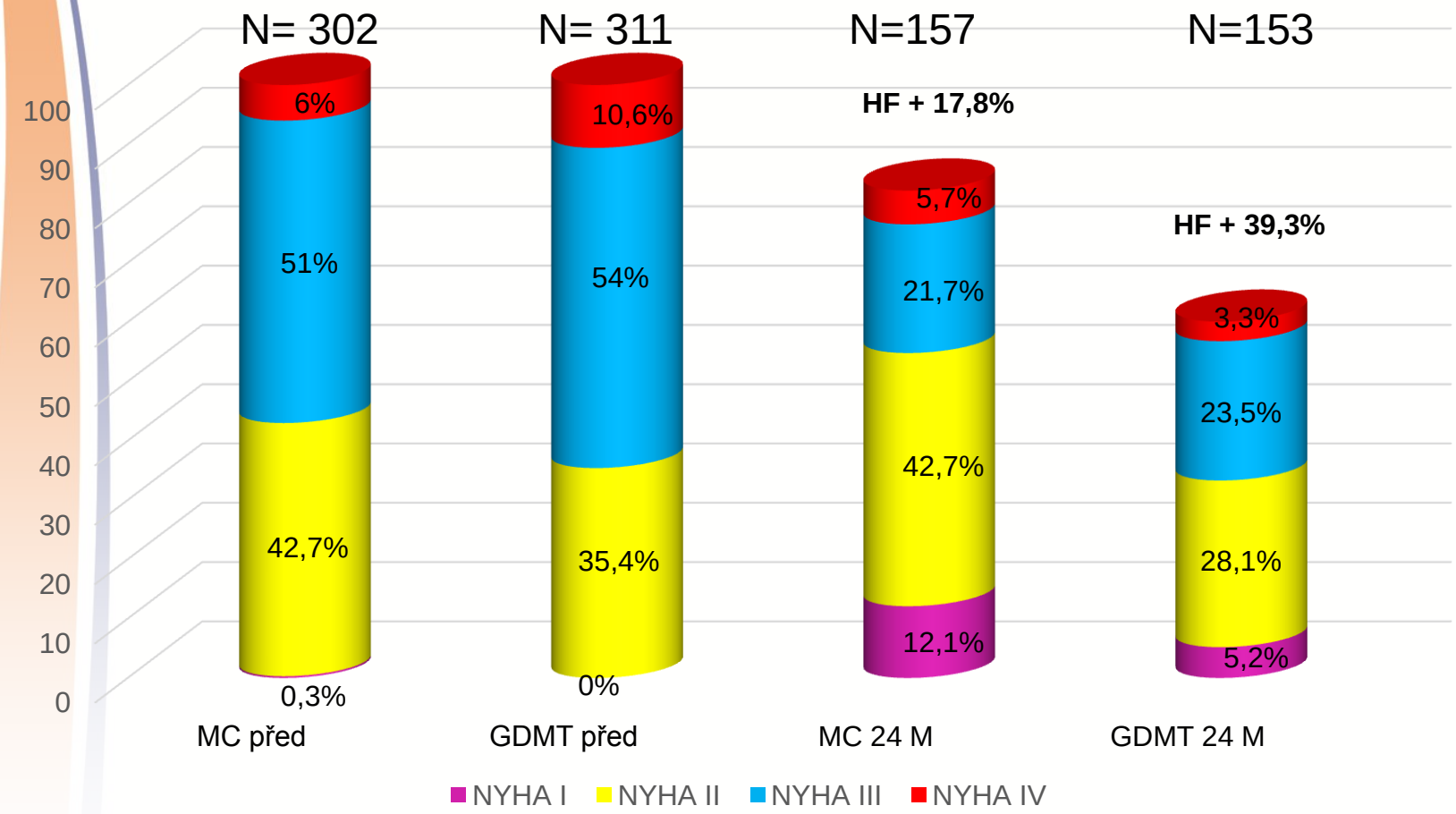
VÝSLEDKY

24-Month Event Rates

	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

VÝSLEDKY

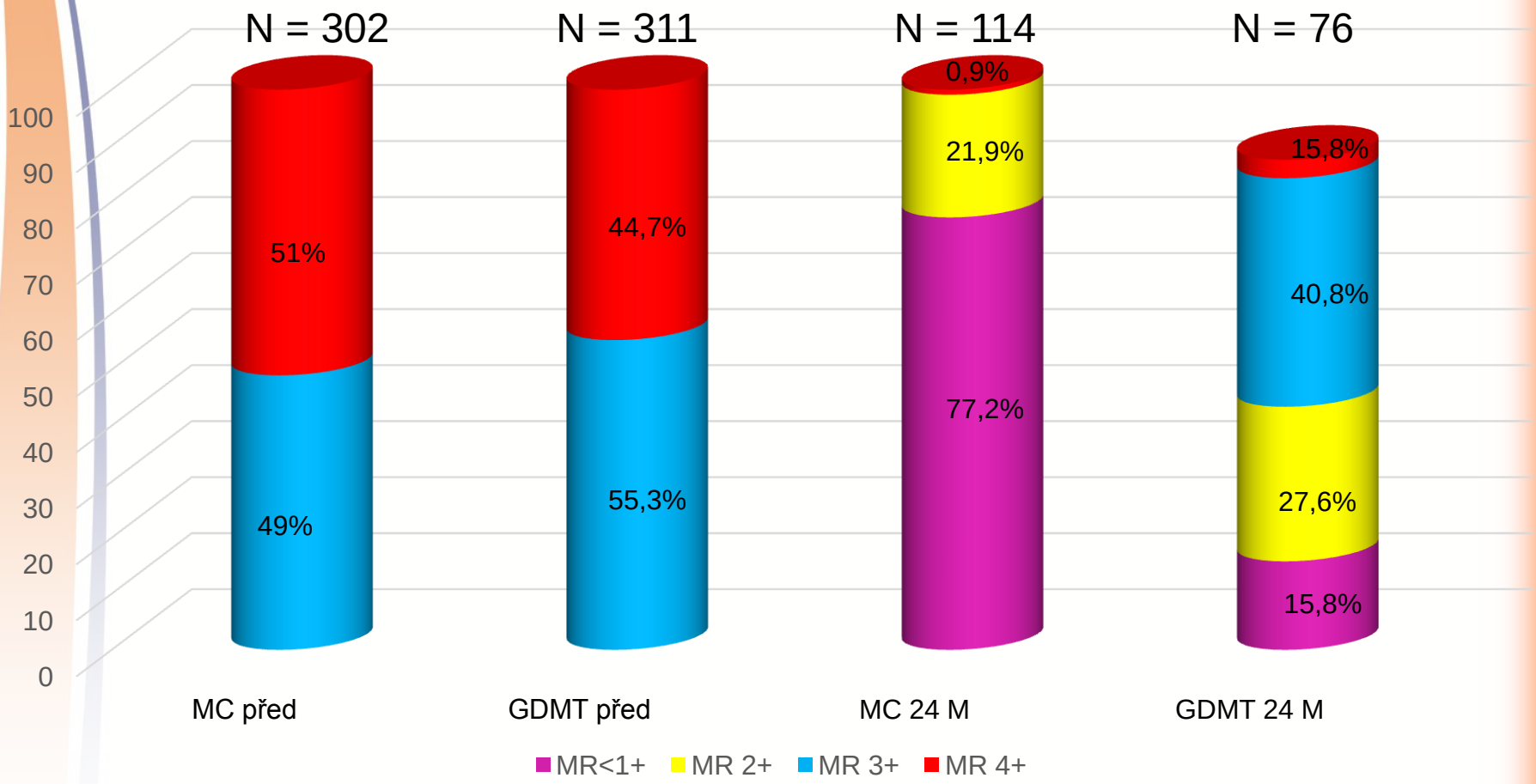
NYHA FUNKČNÍ KAPACITA VE 24 M



COAPT TRIAL

VÝSLEDKY

Mitrální regurgitace ve 24 M (ECHO lab)



COAPT TRIAL

ZÁVĚRY

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*


Děkuji za Vaši pozornost