COAPT TRIAL

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Three-Year Outcomes from a Randomized Trial of Transcatheter Mitral Valve Leaflet Approximation in Patients with Heart Failure and Secondary Mitral Regurgitation

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On behalf of the COAPT Investigators

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Disclosure Statement

- Abbott – Co-PI COAPT Trial
- Edwards Lifesciences- Co-PI PARTNER 3 Trial
- Medtronic- Study Chair-Apollo Trial
- Gore- Consultant

The COAPT (NCT01626079) study was sponsored by Abbott

Background

- In the COAPT trial, treatment of symptomatic patients with heart failure (HF) and severe secondary MR with the MitraClip improved survival at 2 years, reduced HF hospitalizations (HFH), and improved quality of life compared to maximally-tolerated guideline-directed medical therapy (GDMT) alone
- Per protocol, subjects randomized to GDMT were not allowed to crossover to the MitraClip prior to 24 months, but were permitted to do so **after 24 months**

Objectives

The present study sought to:

1) Describe the 3-year clinical outcomes of pts enrolled in the COAPT trial, including those who crossed over to MitraClip (ITT)
2) Analyze the impact of MitraClip crossovers in pts assigned to GDMT alone

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The COAPT Trial

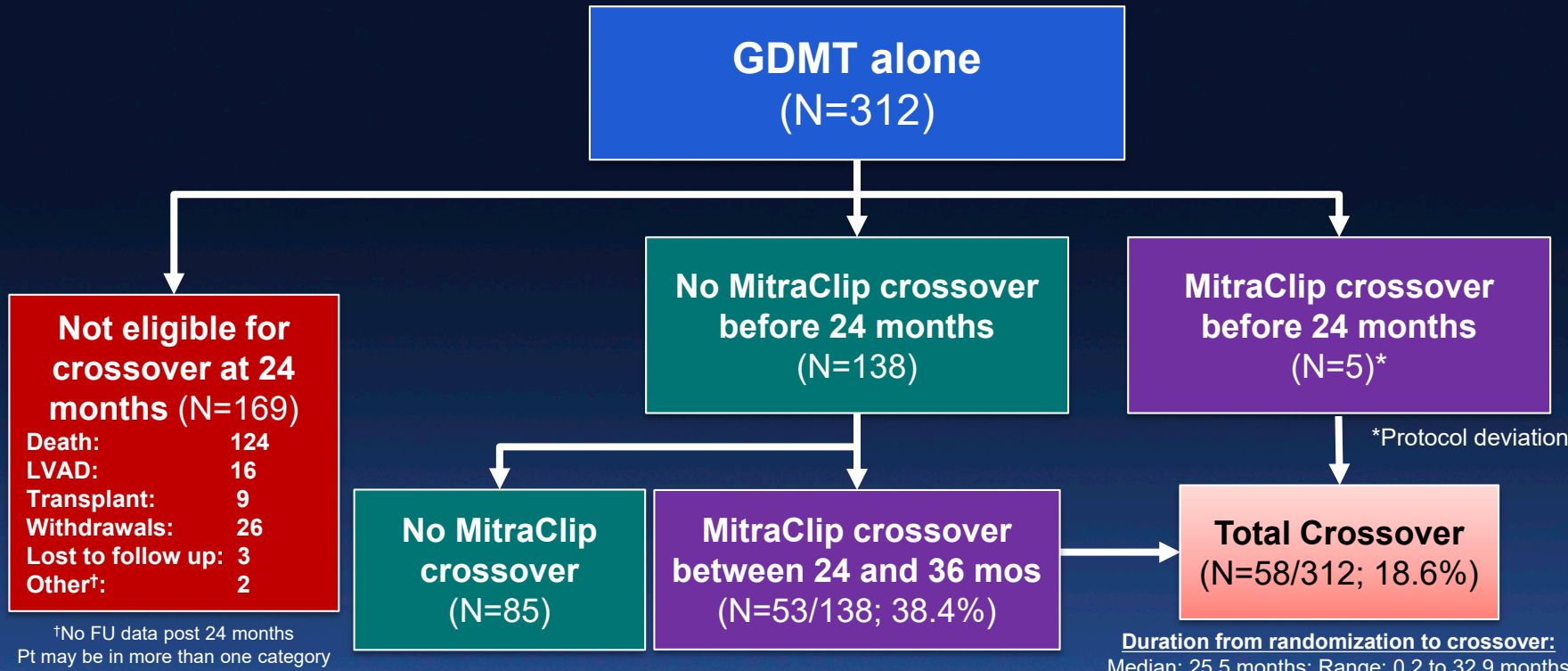
Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation

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

Follow-up at 30d, 6mo, 1y, 18mo, 2y, 3y, 4y, 5y

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

MitraClip Crossovers in GDMT-Assigned Patients



†No FU data post 24 months
Pt may be in more than one category

Duration from randomization to crossover:
Median: 25.5 months; Range: 0.2 to 32.9 months

Follow-up after crossover:
Median: 7.7 months; Range: 0.0 to 43.6 months

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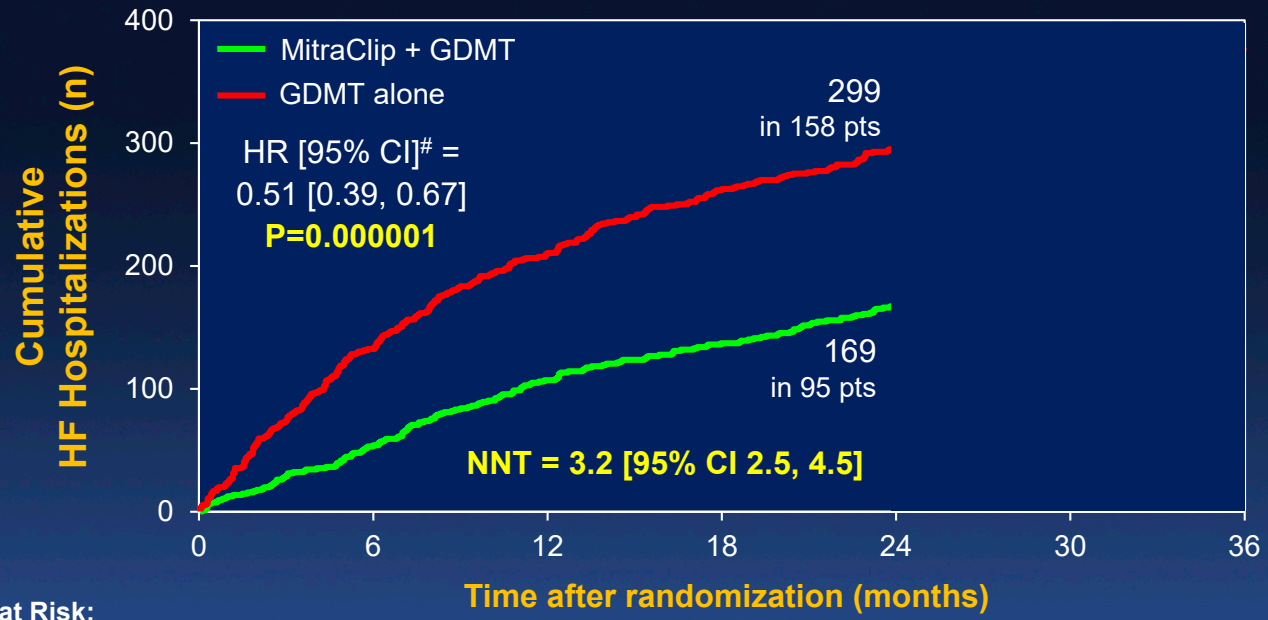
Primary Effectiveness Endpoint

All Hospitalizations for HF within 36 months

All patients, ITT, including crossovers



# at Risk:					
MitraClip + GDMT	302	269	238	219	189
GDMT alone	312	272	223	185	144

#Joint frailty model

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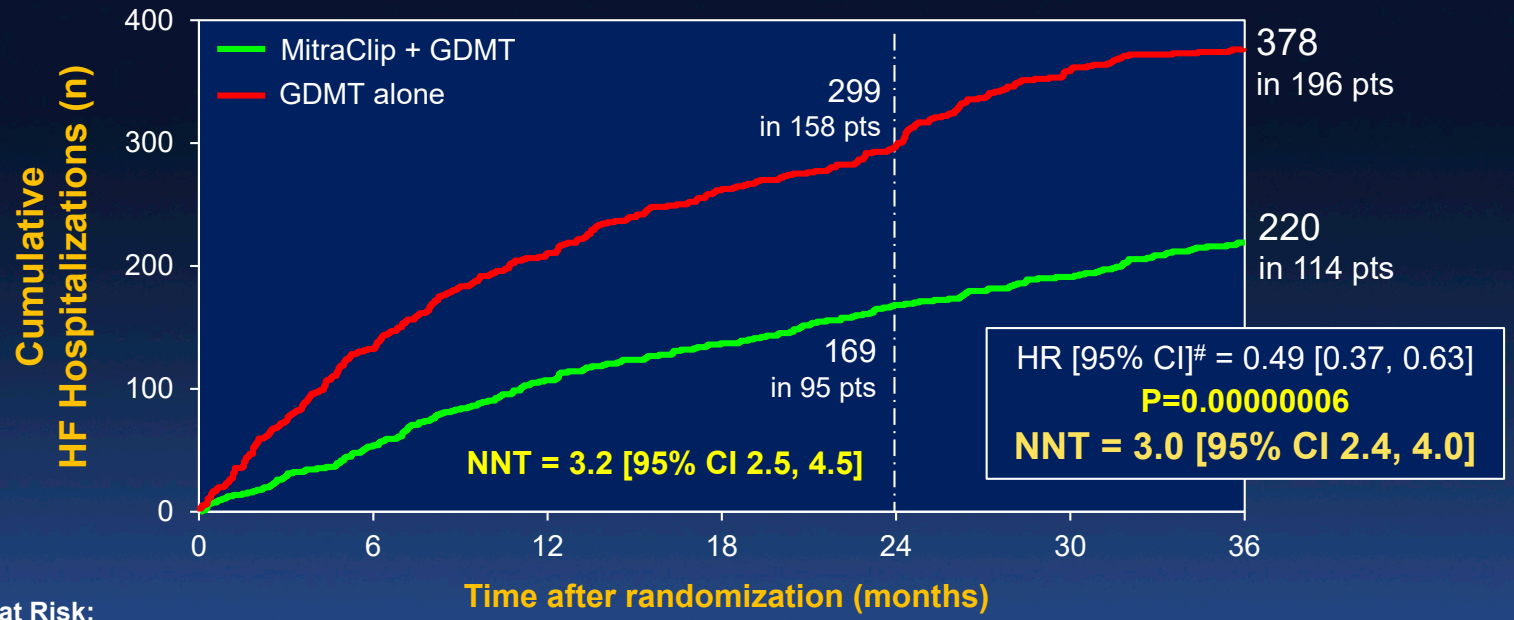
Primary Effectiveness Endpoint

All Hospitalizations for HF within 36 months

All patients, ITT, including crossovers



# at Risk:							
MitraClip + GDMT	302	269	238	219	189	128	93
GDMT alone	312	272	223	185	144	89	68

#Joint frailty model

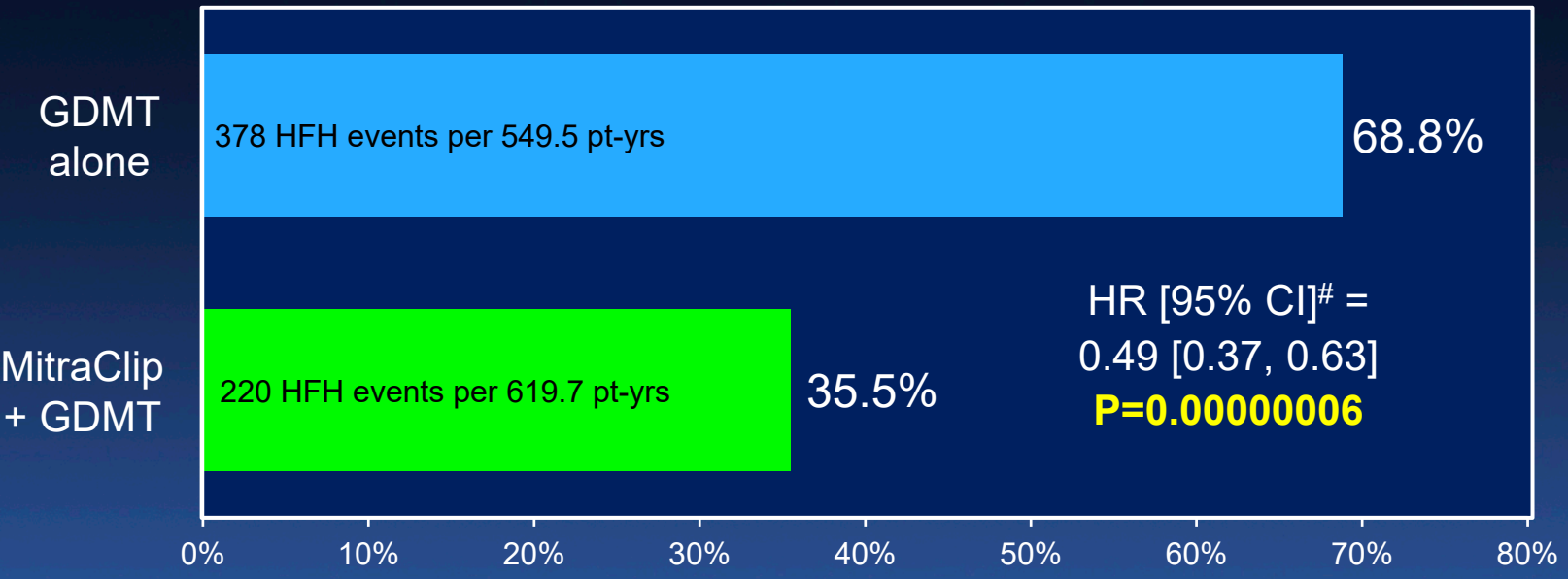
COAPT TRIAL

Primary Effectiveness Endpoint

Annualized Rates of HF Hospitalizations within 36 months

All patients, ITT, including crossovers

NNT= 3.0 [95% CI 2.4, 4.0]



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Annualized rate is calculated as total number of HF Hospitalization events divided by total follow-up years

#Joint frailty model

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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)

Event rates are Kaplan-Meier time-to-first event estimates;
Includes only first occurrence of each event

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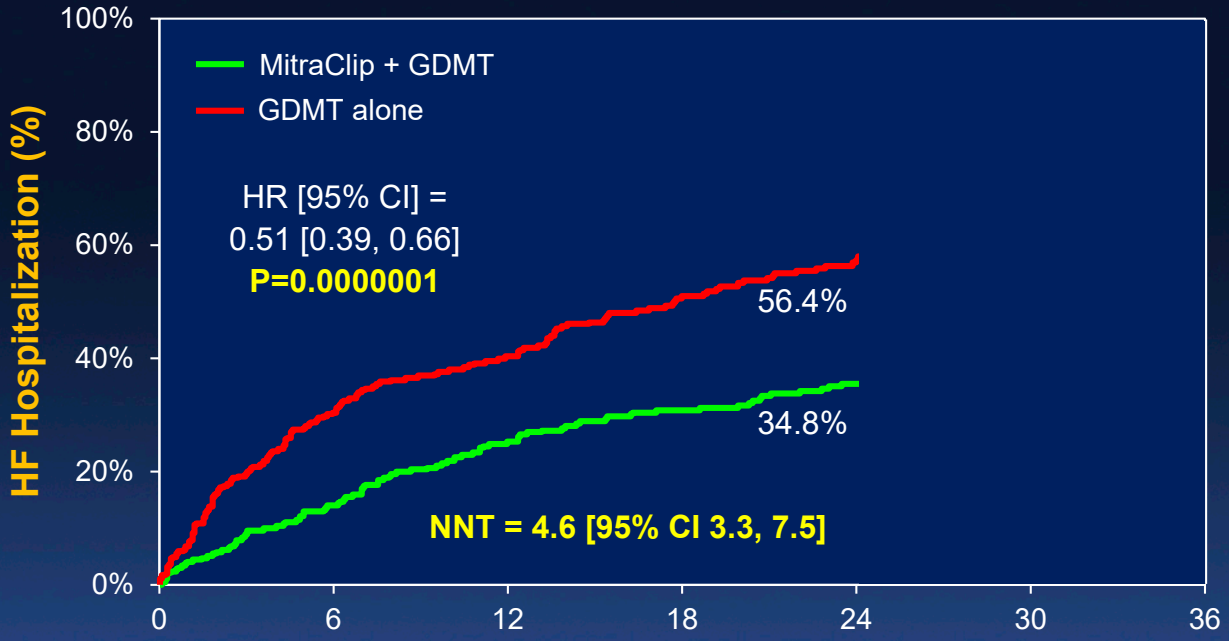
First Heart Failure Hospitalization

All patients, ITT, including crossovers



# at Risk:					
MitraClip + GDMT	302	238	196	176	148
GDMT alone	312	206	156	120	87

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Event rates are Kaplan-Meier time-to-first event estimates

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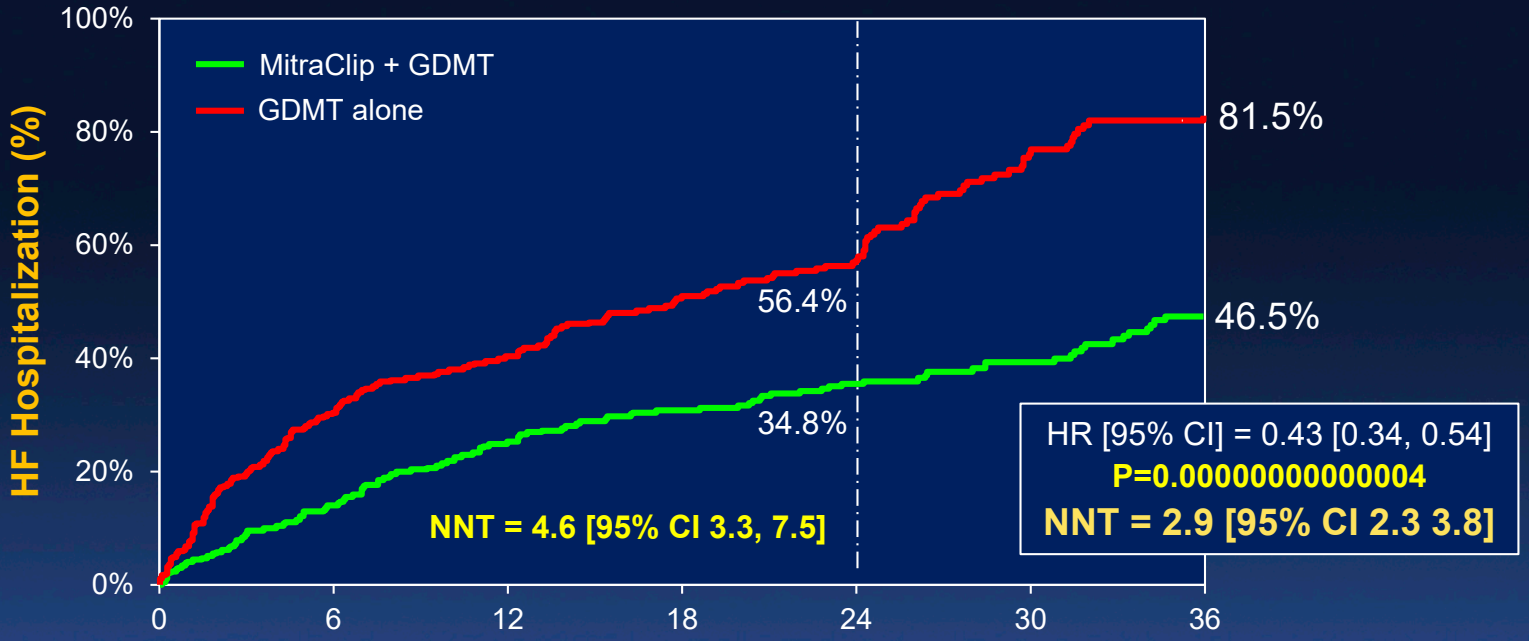
COAPT TRIAL

First Heart Failure Hospitalization

All patients, ITT, including crossovers



# at Risk:							
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GDMT alone	312	206	156	120	87	37	20

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Event rates are Kaplan-Meier time-to-first event estimates

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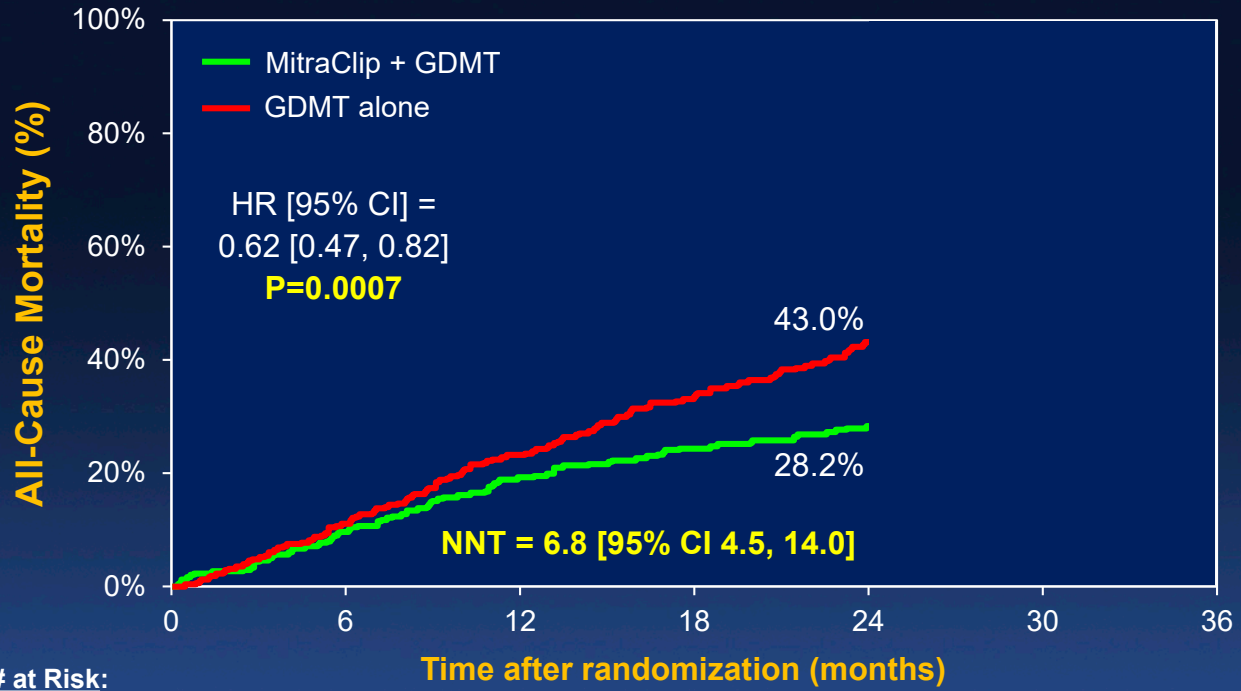
All-Cause Mortality

All patients, ITT, including crossovers



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Event rates are Kaplan-Meier time-to-first event estimates

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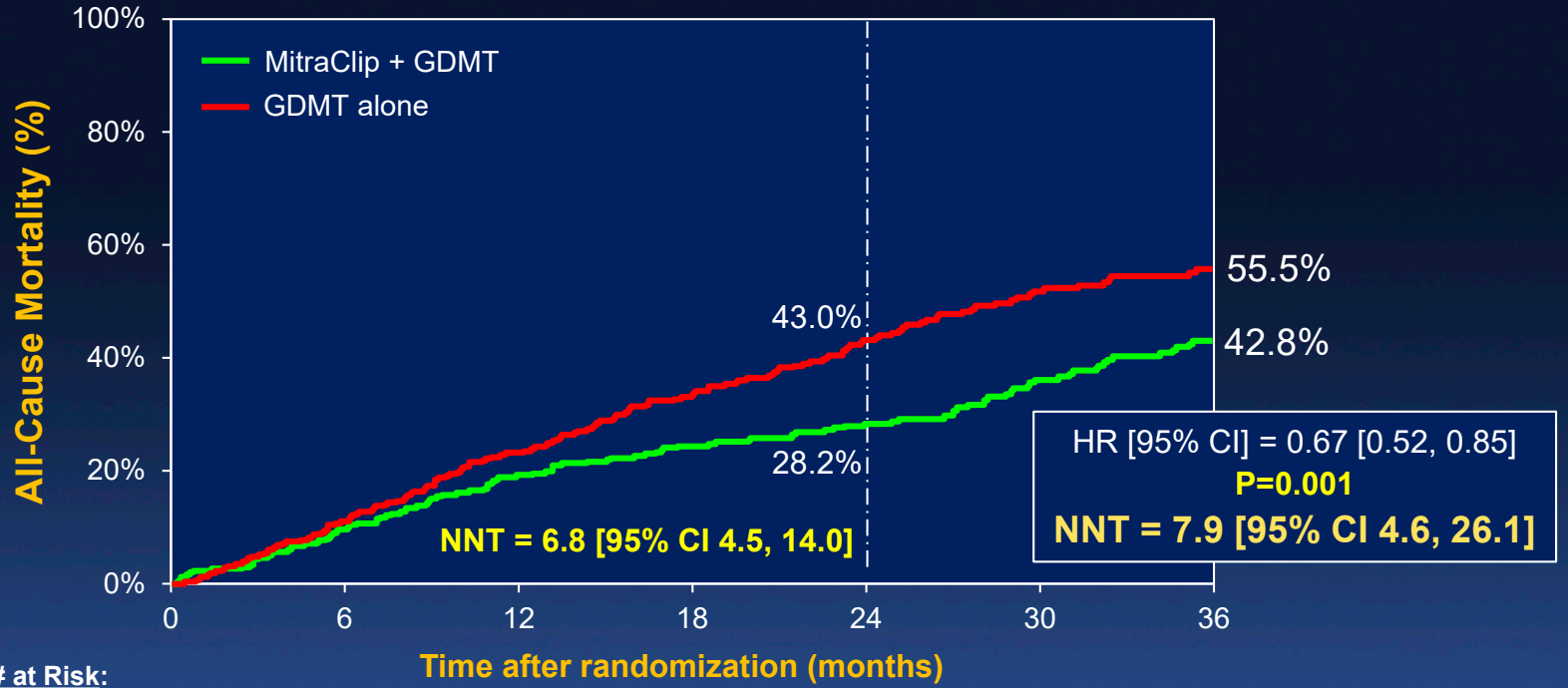
COAPT TRIAL

All-Cause Mortality

All patients, ITT, including crossovers



# at Risk:							
MitraClip + GDMT	302	269	238	219	189	128	93
GDMT alone	312	272	223	186	145	91	70

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Event rates are Kaplan-Meier time-to-first event estimates

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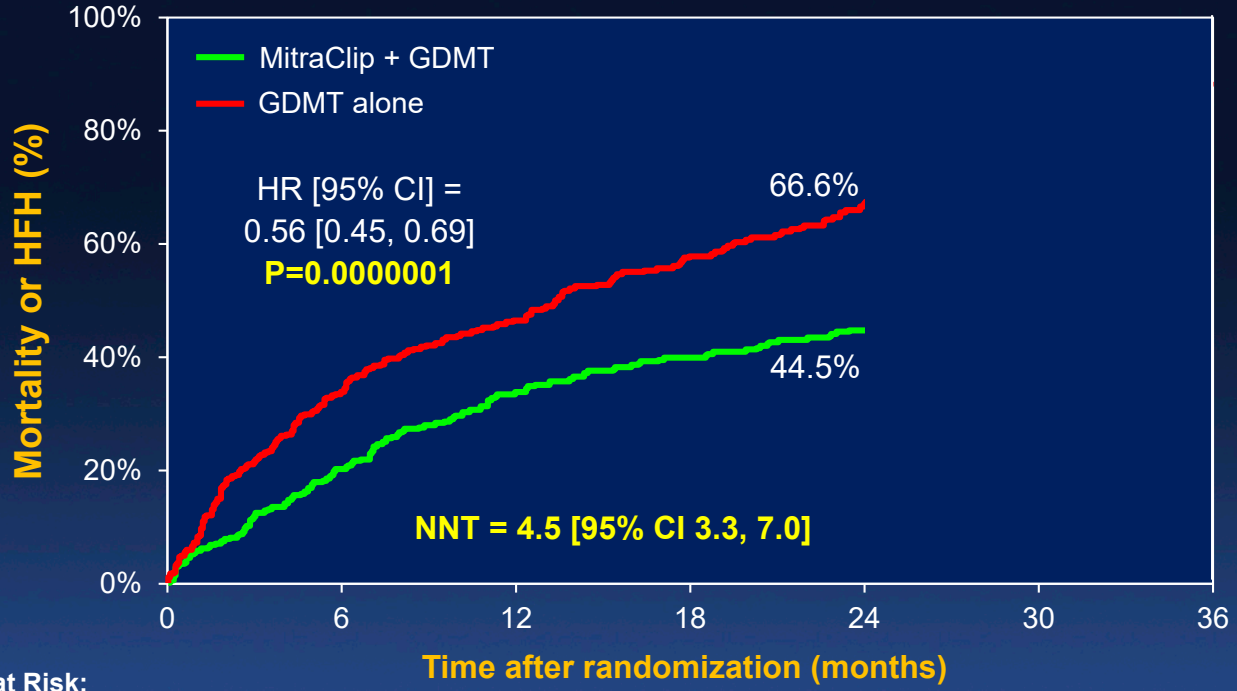
All-Cause Mortality or HF Hospitalization

All patients, ITT, including crossovers



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Event rates are Kaplan-Meier time-to-first event estimates

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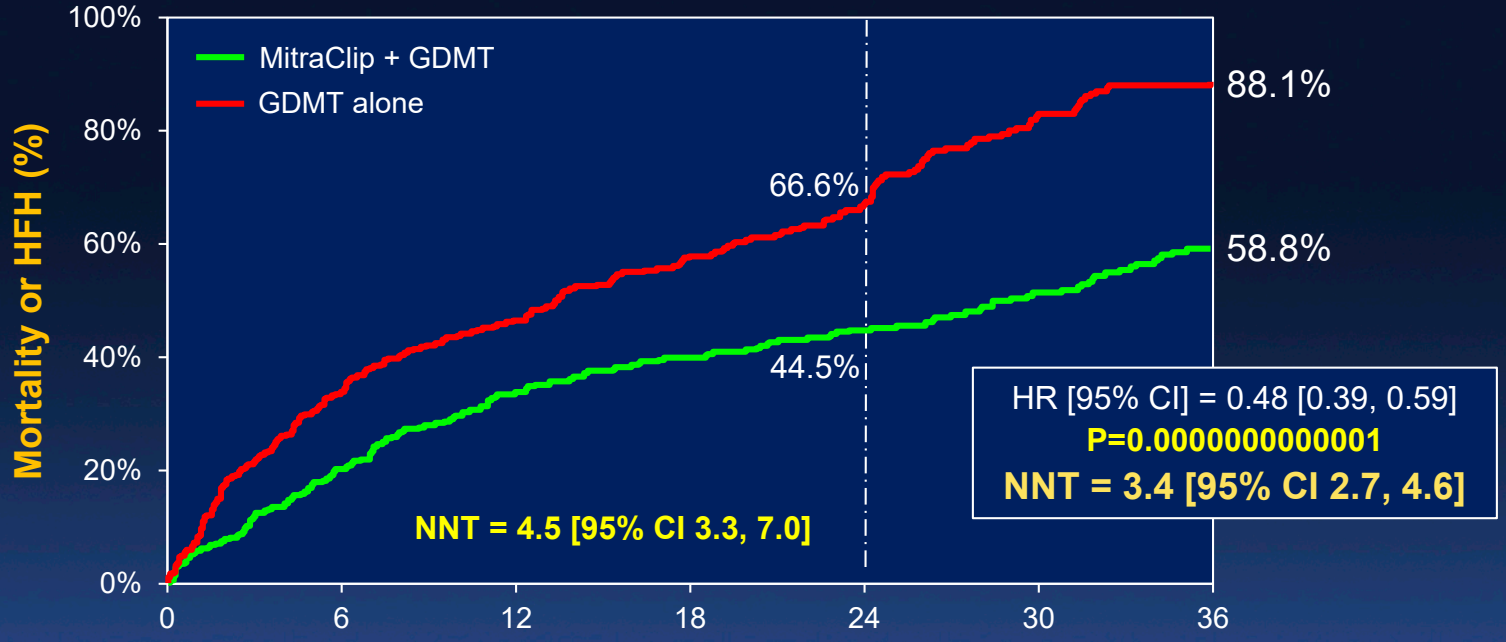
All-Cause Mortality or HF Hospitalization

All patients, ITT, including crossovers



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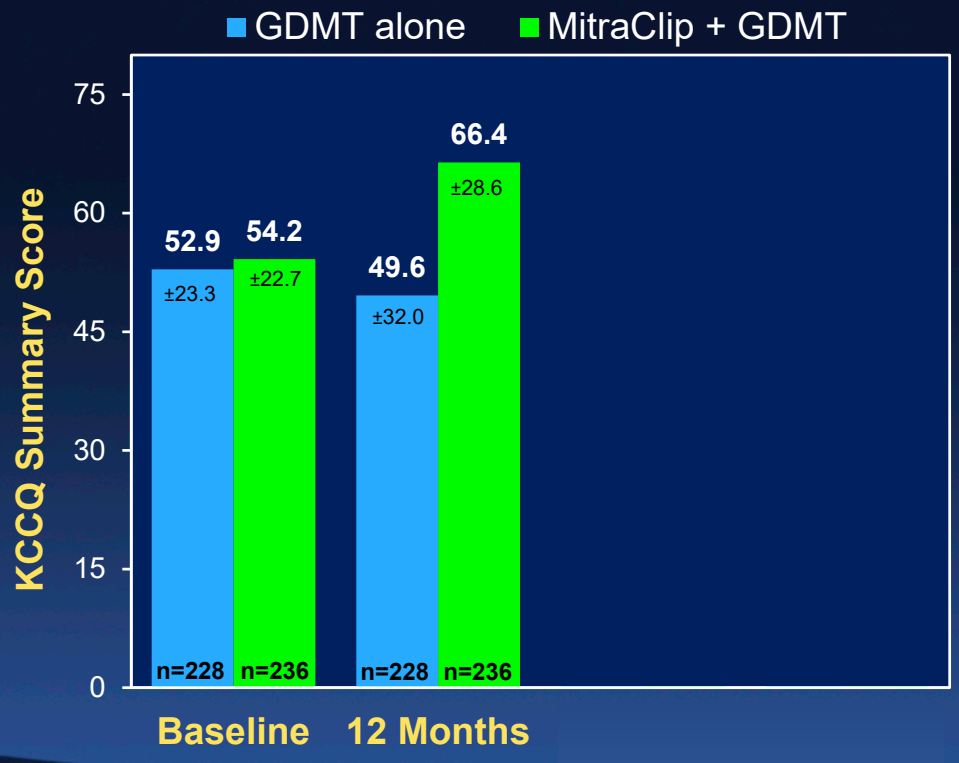
GDMT alone	312	206	156	120	87	37	20

Event rates are Kaplan-Meier time-to-first event estimates

KCCQ Summary Score

All patients, ITT, 24 months



Pts with adjudicated HF death are assigned KCCQ score of 0 at 24 months.
*ANCOVA model with baseline KCCQ and treatment effect as covariates

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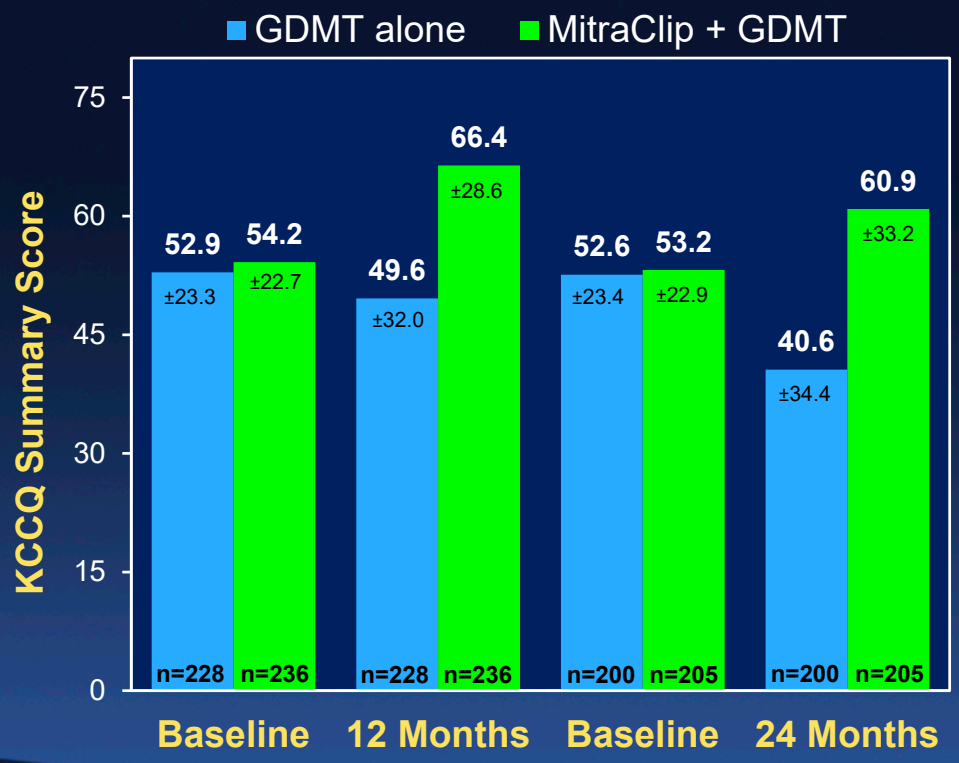
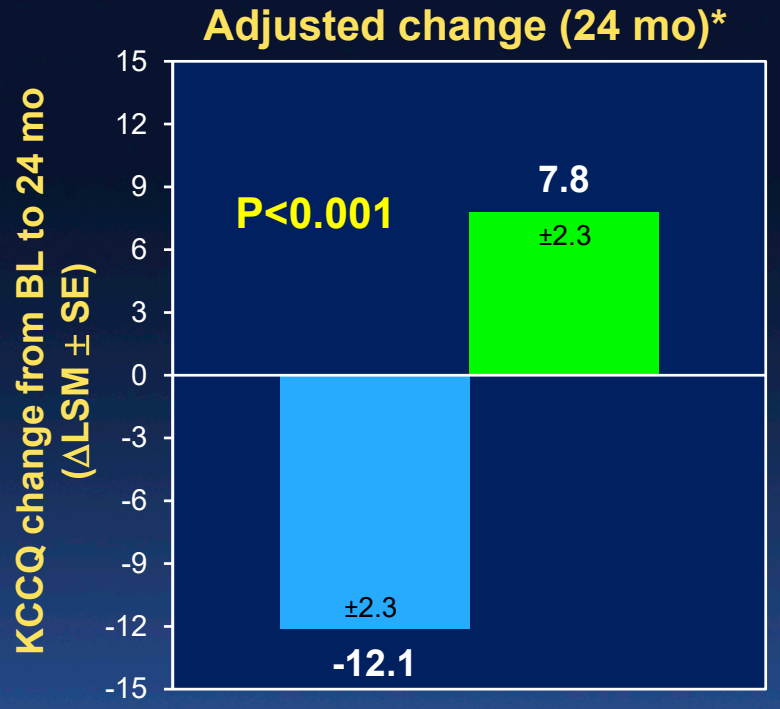
KCCQ Summary Score

All patients, ITT, 24 months





Pts with adjudicated HF death are assigned KCCQ score of 0 at 24 months.
*ANCOVA model with baseline KCCQ and treatment effect as covariates

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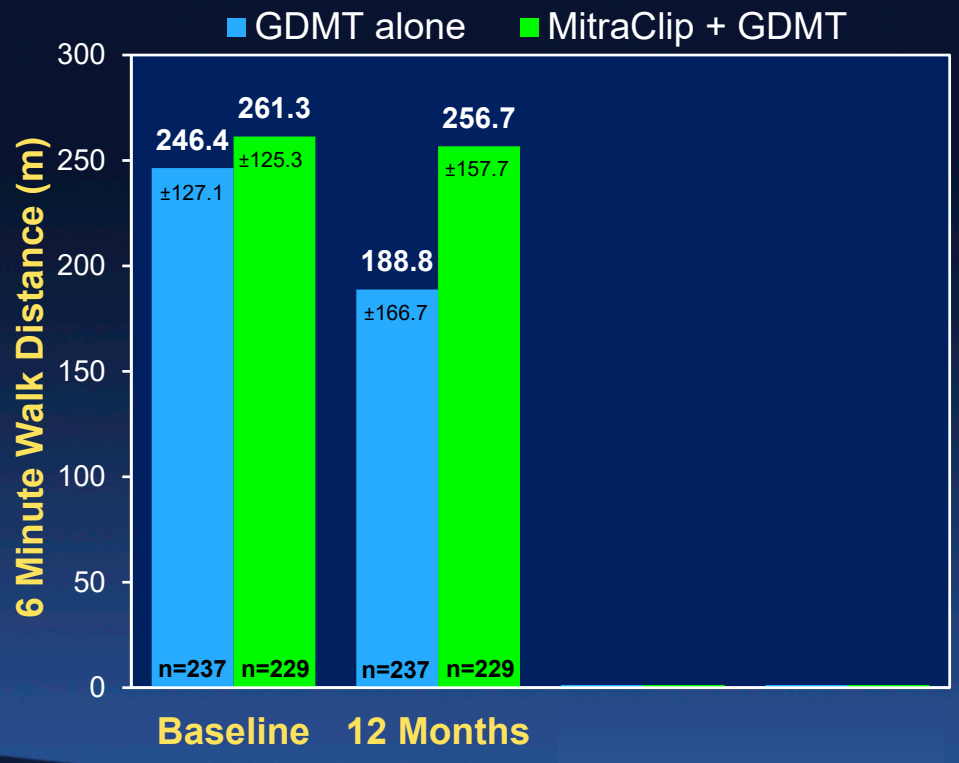
6MWD Outcomes

All patients, ITT, 24 months



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Pts with adjudicated HF death or unable to walk due to cardiac reasons are assigned 6MWD of 0 at 24 months. *ANCOVA model with baseline 6MWD and treatment effect as covariates

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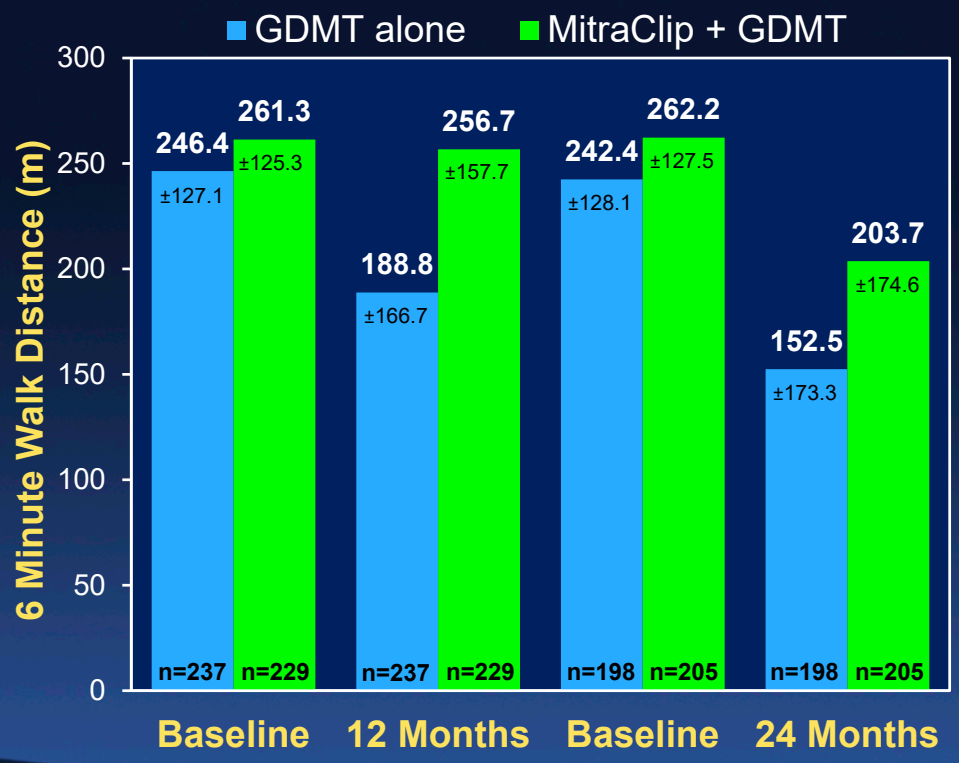
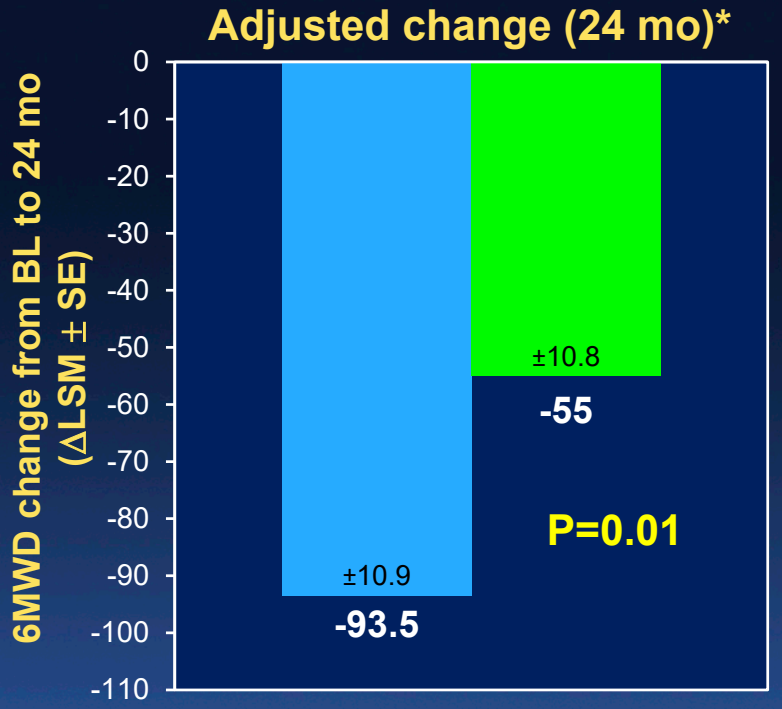
6MWD Outcomes

All patients, ITT, 24 months





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Pts with adjudicated HF death or unable to walk due to cardiac reasons are assigned 6MWD of 0 at 24 months. *ANCOVA model with baseline 6MWD and treatment effect as covariates

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Adverse Event Rates (i)

All patients, ITT, 36 months

	MitraClip + GDMT (n=302)	GDMT alone (n=312)	HR [95% CI]	P-value
Death, all-cause	42.8%	55.5%	0.67 [0.52, 0.85]	0.001
- CV	36.0%	47.4%	0.65 [0.49, 0.85]	0.002
- HF-related	21.6%	34.7%	0.51 [0.35, 0.74]	0.004
- Non-HF-related	18.4%	19.8%	0.88 [0.58, 1.34]	0.55
- Non-CV	10.6%	15.5%	0.74 [0.43, 1.27]	0.27
Hospitalization, all-cause	77.7%	93.3%	0.70 [0.58, 0.84]	<0.001
- CV	64.6%	86.7%	0.58 [0.48, 0.72]	<0.001
- HF-related	46.5%	81.5%	0.43 [0.34, 0.54]	<0.001
- Non-HF-related	40.8%	40.6%	0.98 [0.73, 1.31]	0.87
- Non-CV	56.9%	62.3%	0.89 [0.71, 1.12]	0.31
Death or HF hospitalization	59.0%	88.0%	0.48 [0.39, 0.59]	<0.001
CV Death or HF hospitalization	54.6%	85.1%	0.47 [0.38, 0.58]	<0.001

Event rates are Kaplan-Meier time to first event estimates (n of events)

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Adverse Event Rates (ii)

All patients, ITT, 36 months

	MitraClip + GDMT (n=302)	GDMT alone (n=312)	HR [95% CI]	P-value
MV intervention or surgery*	3.8%	49.2%	0.10 [0.05, 0.20]	<0.001
- MitraClip*	3.5%	47.1%	0.10 [0.05, 0.20]	<0.001
- Mitral valve surgery	0.4%	3.3%	0.12 [0.02, 0.97]	0.05
PCI or CABG	4.0%	4.9%	0.70 [0.29, 1.66]	0.42
- PCI	4.0%	4.3%	0.83 [0.34, 2.05]	0.69
- CABG	0.0%	0.7%	-	1.0
Stroke	7.7%	9.8%	0.80 [0.41, 1.57]	0.51
MI	7.7%	13.3%	0.65 [0.35, 1.23]	0.19
New CRT implant	3.4%	3.1%	0.96 [0.36, 2.56]	0.93
LVAD or heart transplant	7.3%	11.4%	0.49 [0.25, 0.94]	0.03
- LVAD	5.4%	8.6%	0.48 [0.22, 1.04]	0.06
- Heart transplant	2.6%	4.9%	0.45 [0.15, 1.30]	0.14

Event rates are Kaplan-Meier time to first event estimates (n of events)

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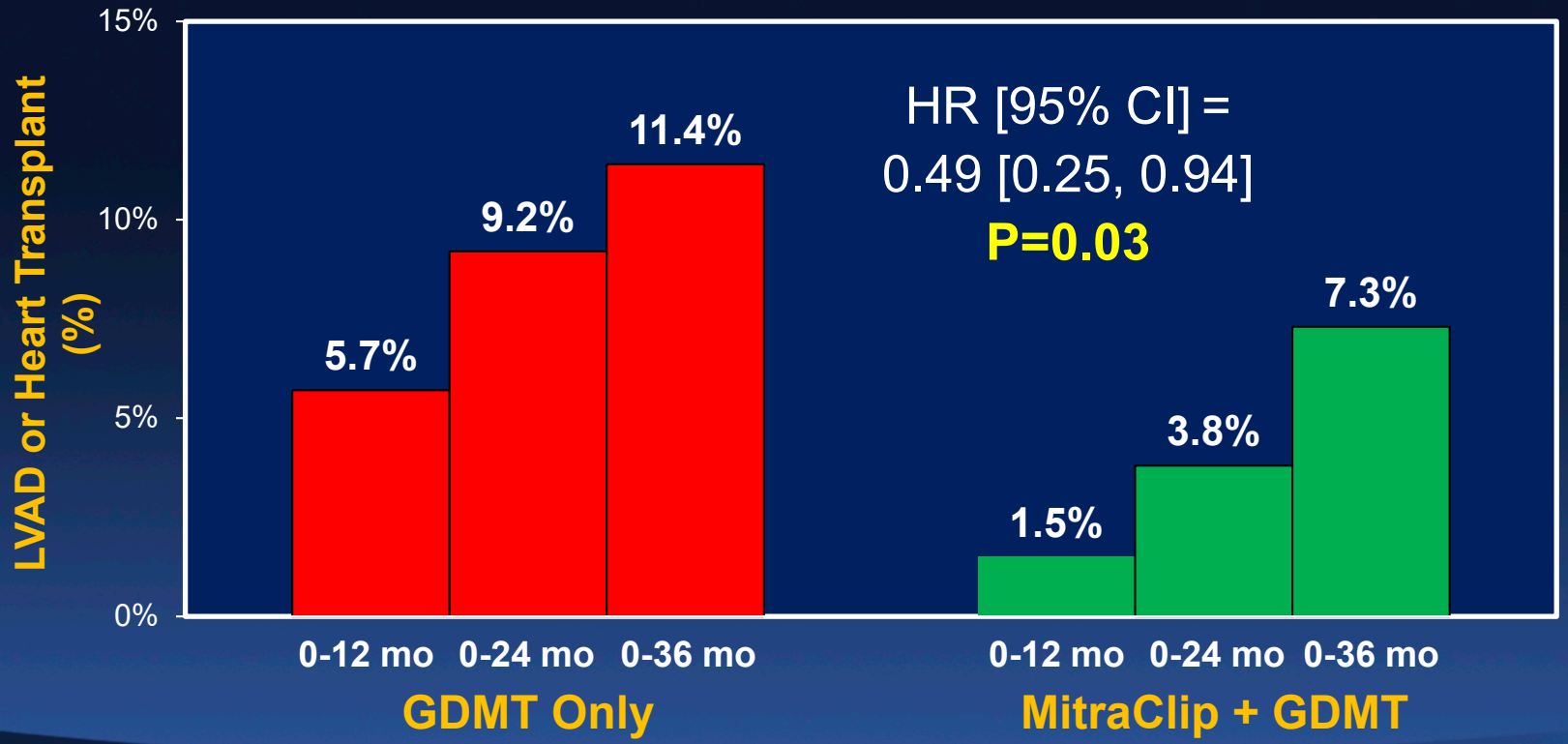
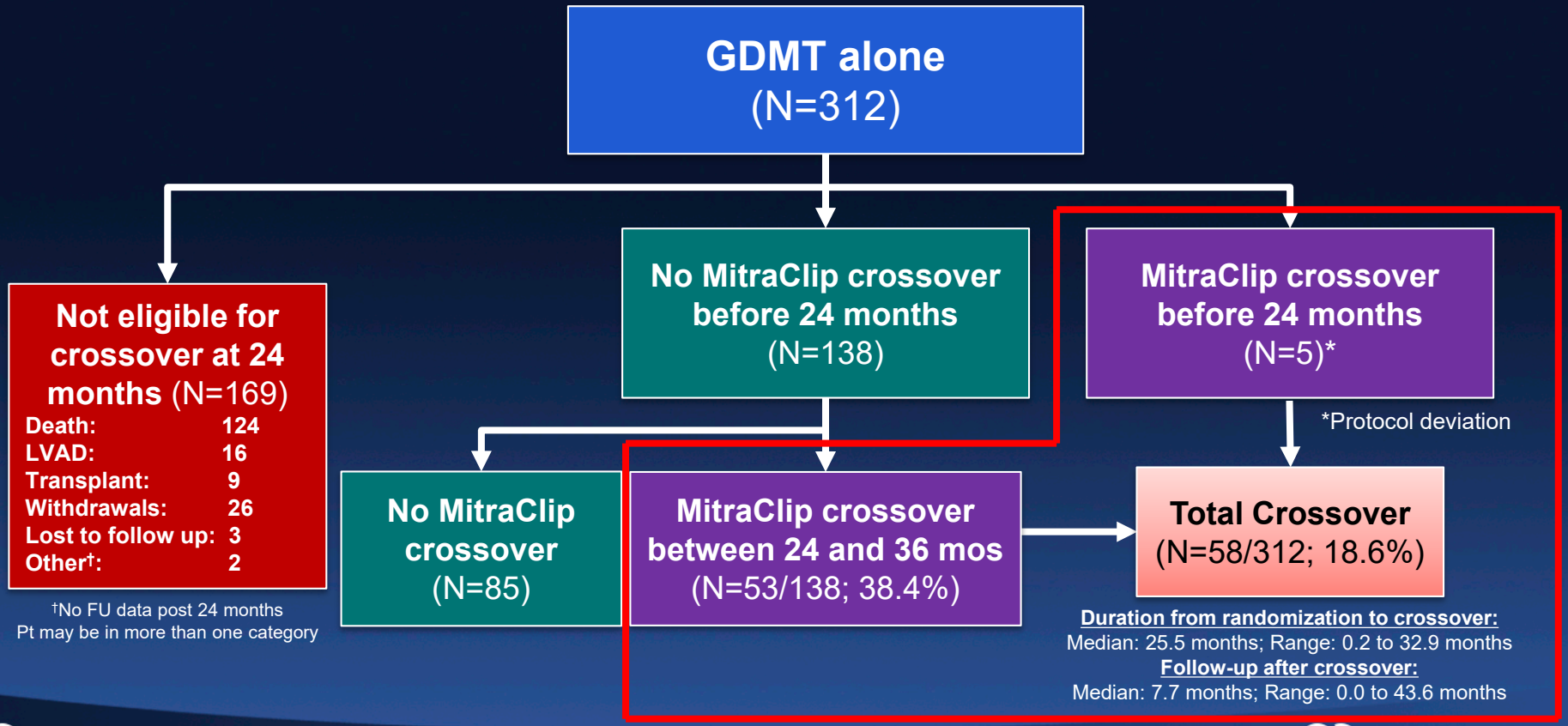
LVAD or Heart Transplantation

All patients, ITT, including crossovers



Event rates are Kaplan-Meier time-to-first event estimates

MitraClip Crossovers in GDMT-Assigned Patients



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MitraClip Procedure Outcomes

(All pts undergoing a MitraClip procedure)

	MitraClip + GDMT (N=302)	GDMT alone, MitraClip crossovers (N=58)	P-value
MitraClip procedure attempted	293/302 (97.0%)	58/58 (100%)	
Clip implanted (MitraClip procedure attempted)	287/293 (98.0%)	55/58 (94.8%)	0.17
Clip implanted (all patients)	287/302 (95.0%)	55/58 (94.8%)	
Mean # of clips implanted	1.7 ± 0.7 (n=293)	1.6 ± 0.7 (n=58)	0.56
- 0 clips implanted	6 (2.0%)	3 (5.2%)	0.17
- 1 clip implanted	106 (36.2%)	22 (37.9%)	0.80
- 2 clips implanted	157 (53.6%)	27 (46.6%)	0.33
- 3 clips implanted	23 (7.9%)	6 (10.3%)	0.60
- 4 clips implanted	1 (0.3%)	0 (0.0%)	1.00
Procedure duration (mins)	162.9 ± 118.1 (293)	132.9 ± 50.0 (57)	0.002
- Device procedure time (mins)	118.9 ± 63.5	97.5 ± 46.2 (59)	0.004
- Device time (mins)	82.7 ± 80.8	60.3 ± 34.8 (56)	<0.001
- Fluoroscopy time (mins)	33.9 ± 23.2	30.0 ± 15.5 (51)	0.13

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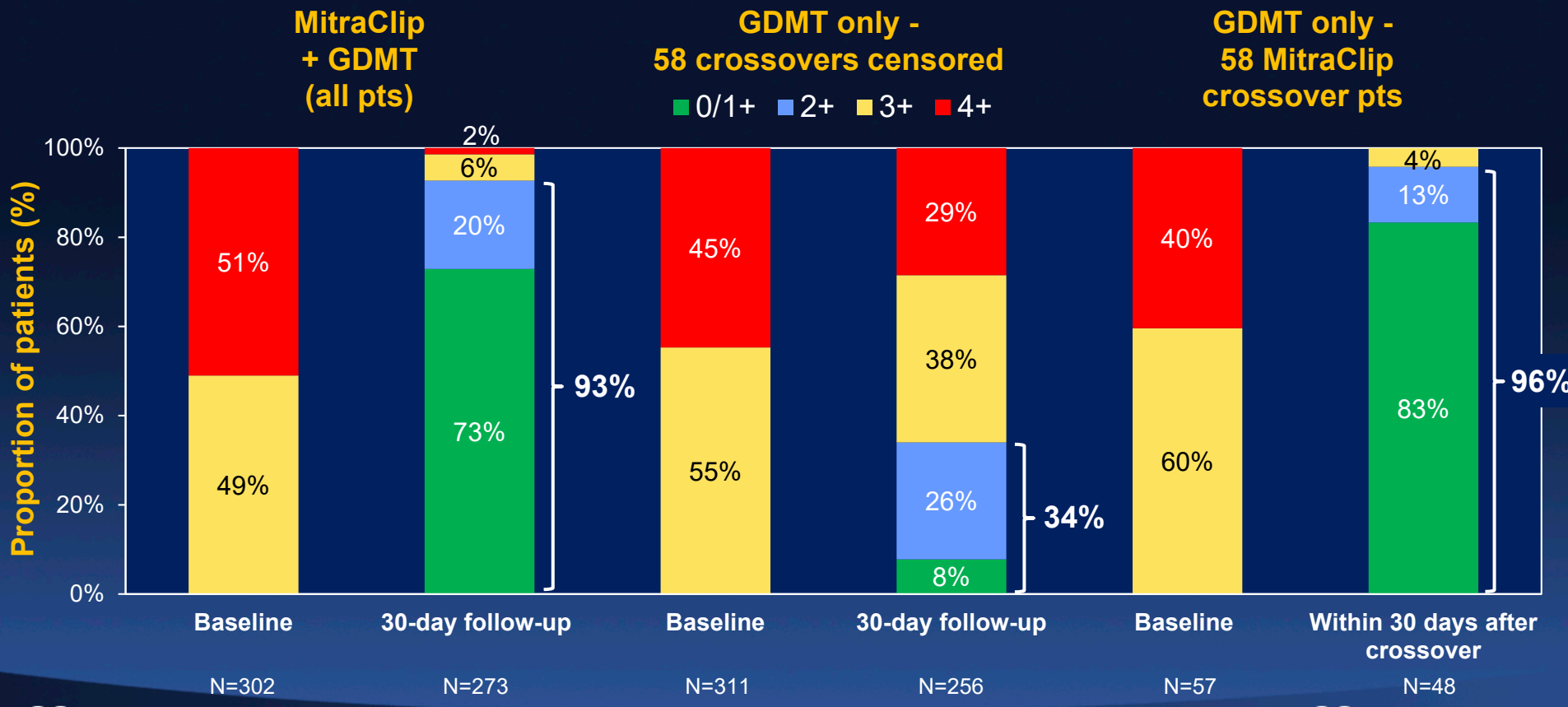
MR Grade at Baseline and 30 Days



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.

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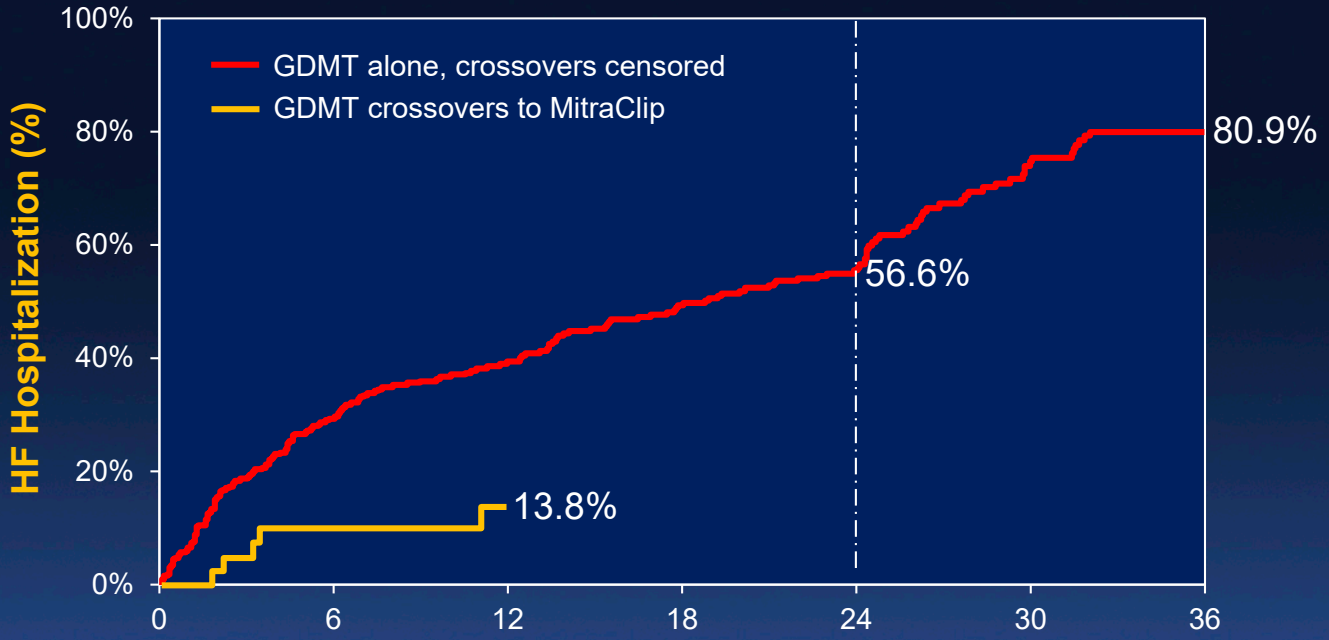
First Heart Failure Hospitalization

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



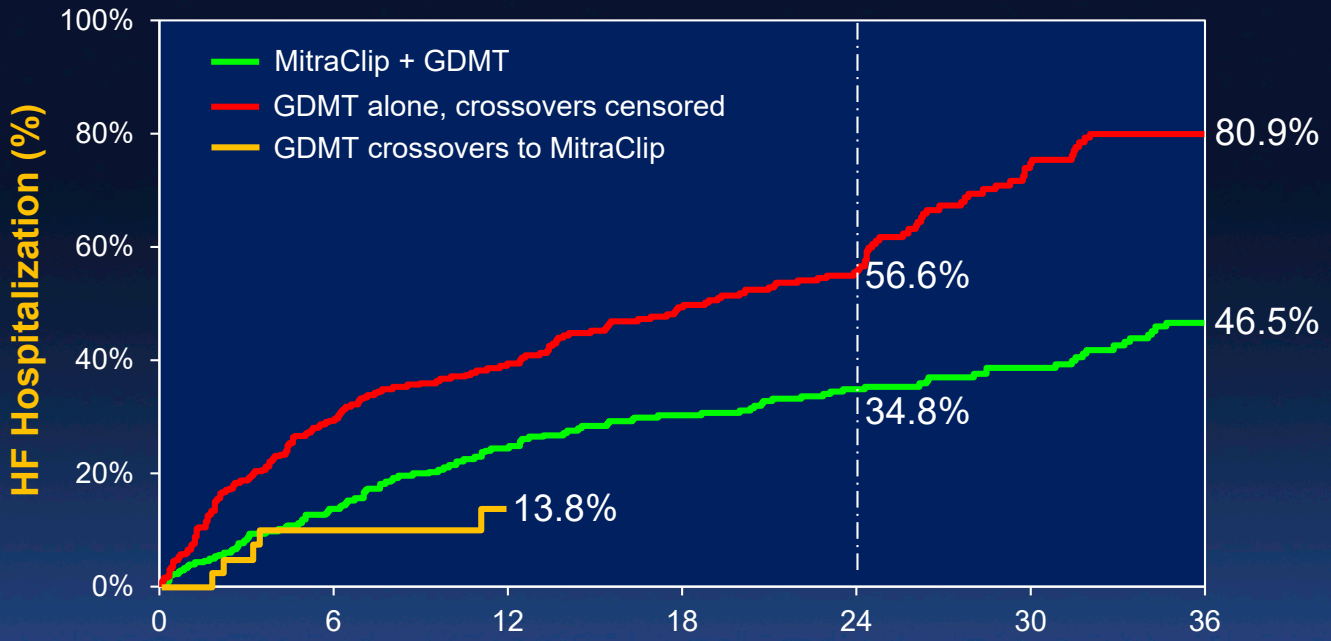
# at Risk:							
GDMT only, crossovers censored	312	205	155	119	85	33	19
GDMT crossovers to MitraClip	58	30	22				

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

COAPT TRIAL

First Heart Failure Hospitalization

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



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Multivariable Predictors of First HFH Within 36 Months

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

	Hazard Ratio [95% CI]	P-Value
Treatment with MitraClip	0.42 [0.22, 0.80]	0.009
Vasodilator use (hydralazine or nitrates)	2.70 [1.90, 3.83]	<0.0001
BNP (per 100 pg/mL)	1.02 [1.01, 1.03]	0.0006
Beta-blocker use	0.52 [0.32, 0.83]	0.006
LVEF (per 10%)	0.79 [0.66, 0.95]	0.01

Variables entered the final model include: ACEi/ARB/ARNI use, age, beta-blocker use, BNP, body surface area, serum creatinine, treatment with MitraClip, vasodilator use (hydralazine or nitrates), KCCQ summary score, LVEDV, LVEF, renal disease, 6MWD, prior stroke, systolic BP, TR grade; other variables tested had α>0.20 in univariable analysis, were colinear with the present variables or had <90% values

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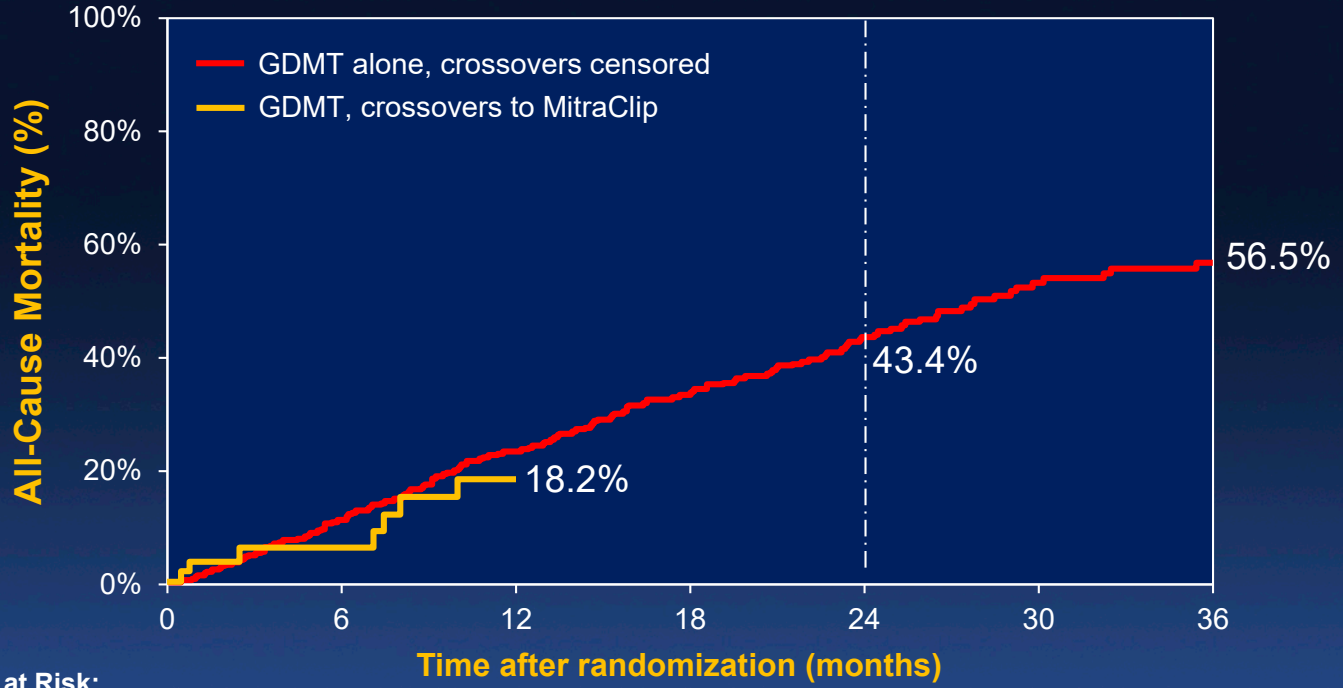
All-Cause Mortality

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



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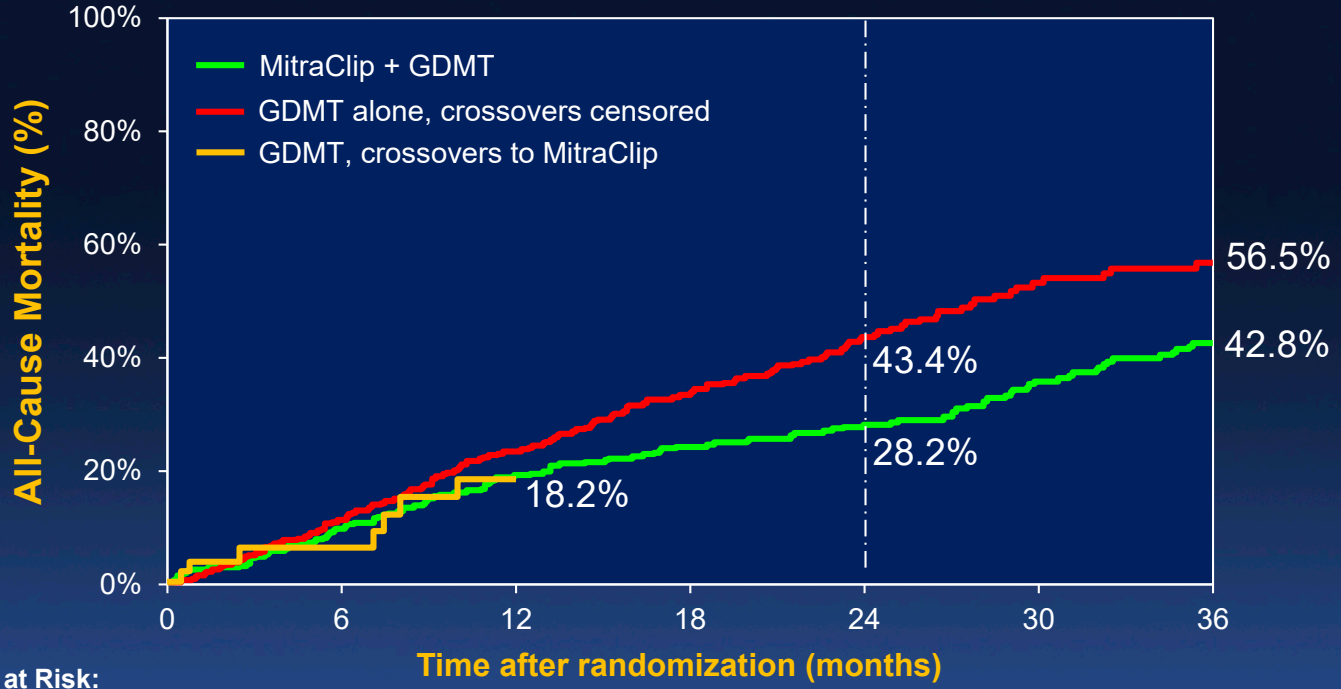
All-Cause Mortality

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



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Multivariable Predictors of Mortality Within 36 Months

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

	Hazard Ratio [95% CI]	P-Value
Treatment with MitraClip	0.89 [0.43, 1.85]	0.76
BNP (per 100 pg/mL)	1.03 [1.02, 1.05]	< 0.0001
EROA (per 10 mm^2)	1.23 [1.10, 1.37]	0.0004
Systolic blood pressure (per 1 mmHg)	0.98 [0.97, 0.99]	0.004
Beta-blocker use	0.47 [0.28, 0.78]	0.004
STS replacement score (per 1 unit)	1.04 [1.01, 1.08]	0.005
6MWD (per 10 meters)	0.98 [0.96, 1.00]	0.01
Female sex	0.62 [0.41, 0.93]	0.02
Serum creatinine (per 1 mg/dL)	1.11 [1.01, 1.22]	0.03
Prior defibrillator implant	0.65 [0.44, 0.97]	0.03

Variables entered the final model include: ACEi/ARB/ARNI use, prior atrial fibrillation, age, aldosterone inhibitor use, history of anemia, beta-blocker use, BNP, serum creatinine, treatment with MitraClip, prior defibrillator implant, diabetes, diastolic BP, EROA, sex, hypertension, KCCQ summary score, prior PCI/CABG, PVD, renal disease, 6MWD, STS replacement score, systolic BP, TR grade, race; other variables tested had α>0.20 in univariable analysis, were colinear with the present variables, or had <90% values

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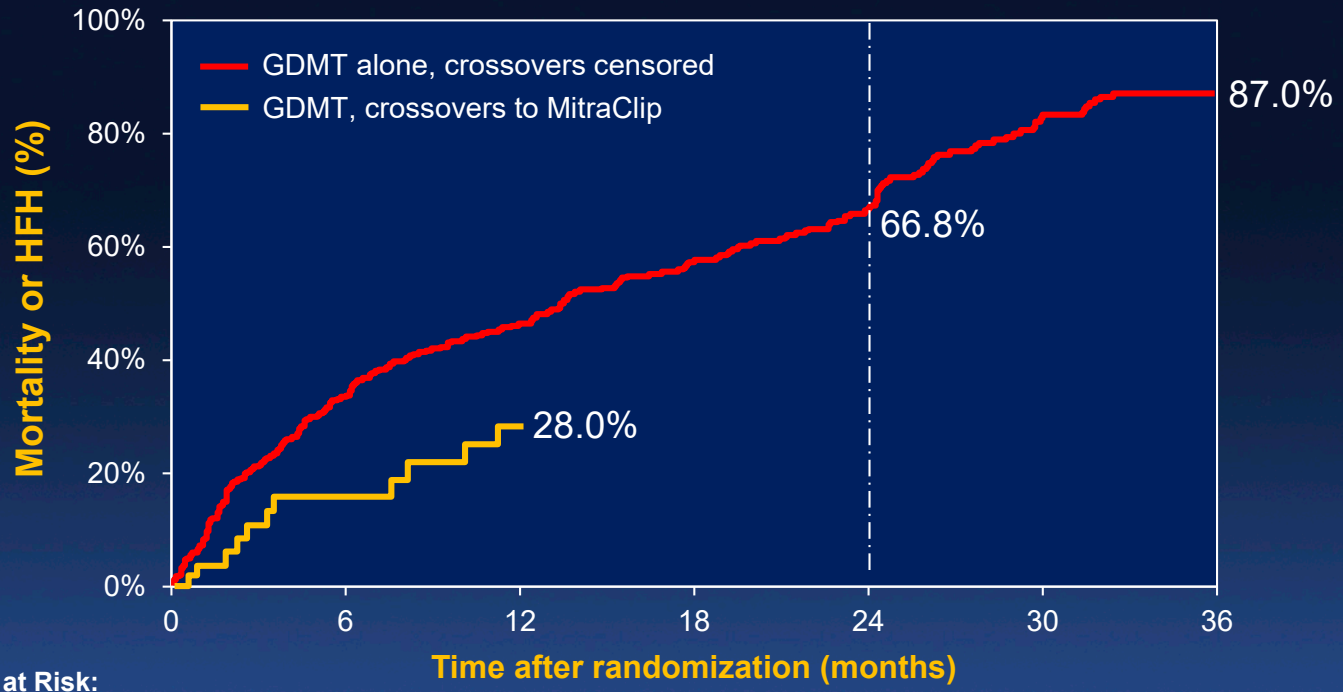
All-Cause Mortality or HF Hospitalization

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



# at Risk:							
GDMT only, crossovers censored	312	205	155	119	85	33	19
GDMT crossovers to MitraClip	58	30	22				

tct2019

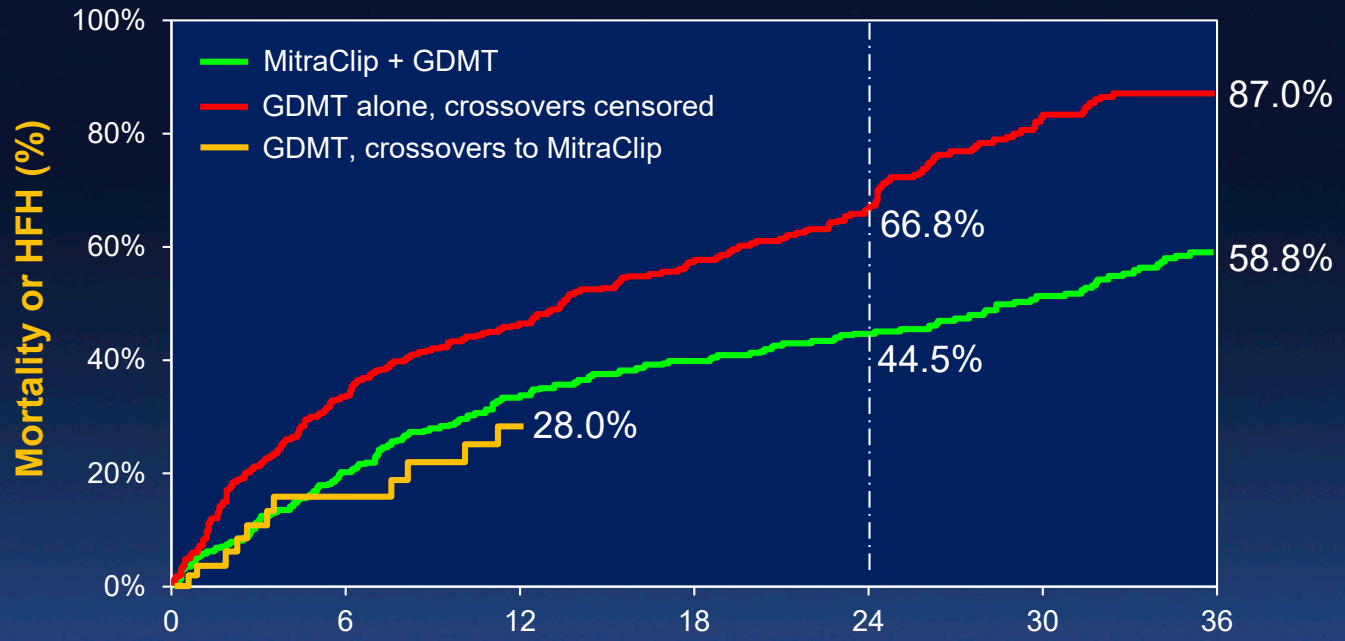
For crossover patients, follow-up duration is from the crossover procedure date; events at procedure dates are excluded.
Event rates are Kaplan-Meier time-to-first event estimates, with landmark analysis for crossover patients

Cardiovascular® Research Foundation

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				

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

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

COAPT TRIAL

Conclusions

In pts with HF and 3+/4+ secondary MR who remained symptomatic despite maximally-tolerated GDMT:

- At 36 months transcatheter mitral leaflet approximation with the MitraClip was safe, provided durable reduction in MR, reduced the rate of HF hospitalizations, and improved survival, QOL and functional capacity compared to GDMT alone
- GDMT only-assigned pts who crossed-over and received a MitraClip experienced fewer HF hospitalizations and deaths or HFHs within 12 months than those who did not crossover, with rates comparable to pts originally assigned to the MitraClip