COAPT TRIAL

COAPT

A Randomized Trial of Transcatheter Mitral Valve Leaflet Approximation in Patients with Heart Failure and Secondary Mitral Regurgitation

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

Disclosure Statement

Gregg W. Stone MD

Consulting fees from Neovasc, Valfix, Ancora, Gore

Equity/options in Ancora

Institutional conflict

Columbia University receives royalties from Abbott for sale of the MitraClip

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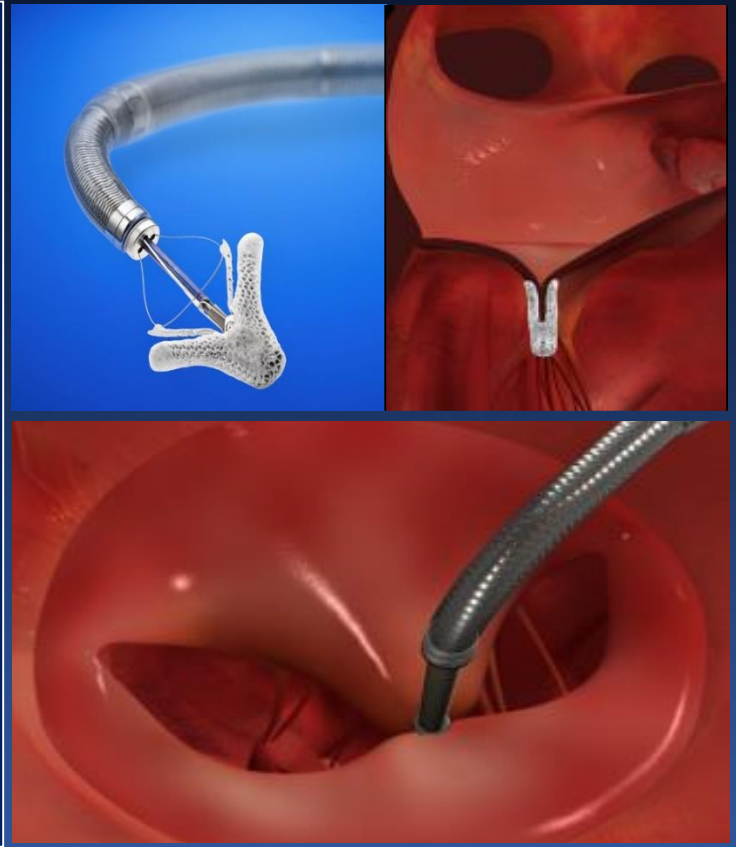
Background (i)

- Pts with heart failure (HF) in whom mitral regurgitation (MR) develops secondary to left ventricular dysfunction have a poor prognosis, with reduced quality-of-life, frequent hospitalizations for heart failure and decreased survival
- There are no proven therapies for secondary MR in HF
  - Guideline-directed medical therapy (GDMT) and cardiac resynchronization therapy (CRT) may provide symptomatic relief in some pts
- Whether correcting secondary MR improves the prognosis of pts with HF is unknown
  - Surgery with a downsized annuloplasty ring has not been demonstrated to be beneficial for secondary MR, and has a high recurrence rate

Background (ii)

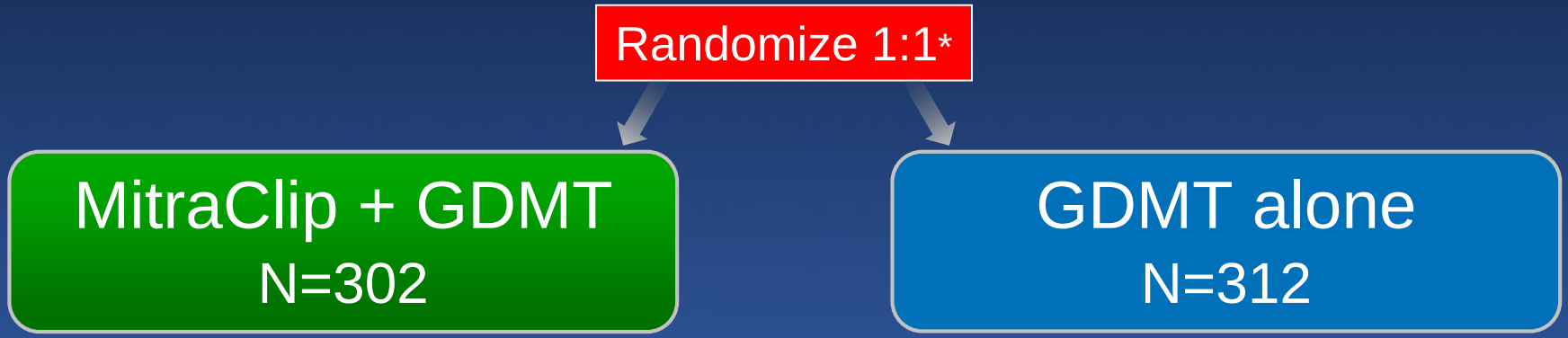
- By approximating the anterior and posterior mitral leaflets and forming a double-orifice valve, the MitraClip device reduces MR
- Registries have suggested that the MitraClip is safe and may provide symptomatic benefit to HF pts with secondary MR
- We therefore performed the COAPT randomized trial to evaluate the safety and effectiveness of transcatheter mitral leaflet approximation in HF pts with secondary MR who remained symptomatic despite GDMT



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

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Key Inclusion Criteria

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

Central Echo Core Lab and Eligibility Committee Review

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

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Primary Endpoints

Primary effectiveness endpoint: All HF hospitalizations through 24 months*

Powered for superiority of the Device group compared with the Control group

Primary safety endpoint: Freedom at 12 mos from device-related complications:

- Single leaflet device attachment
- Device embolization
- Endocarditis requiring surgery
- Echo core laboratory-confirmed mitral stenosis requiring surgery
- Left ventricular assist device implant
- Heart transplant
- Any device-related complication requiring non-elective cardiovascular surgery

Powered for superiority of the Device group vs. a pre-specified OPG**

*Analyzed when the last subject completes 12 months of follow-up; **Objective performance goal

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Baseline Characteristics (i)

	MitraClip + GDMT (N=302)	GDMT alone (N=312)
Age (years)	71.7 ± 11.8	72.8 ± 10.5
Male	66.6%	61.5%
Diabetes	35.1%	39.4%
Hypertension	80.5%	80.4%
Hyperchol.	55.0%	52.2%
Prior MI	51.7%	51.3%
Prior PCI	43.0%	49.0%
Prior CABG	40.1%	40.4%
Prior stroke or TIA	18.5%	15.7%
PVD	17.2%	18.3%
COPD	23.5%	23.1%
H/o atrial fibr	57.3%	53.2%

	MitraClip + GDMT (N=302)	GDMT alone (N=312)
BMI (kg/m^2)	27.0 ± 5.8	27.1 ± 5.9
CrCl (ml/min)	50.9 ± 28.5	47.8 ± 25.0
- ≤60 ml/min	71.6%	75.2%
Anemia (WHO)	59.8%	62.7%
BNP (pg/mL)	1015 ± 1086	1017 ± 1219
NT-proBNP (pg/mL)	5174 ± 6567	5944 ± 8438
STS replacement sc	7.8 ± 5.5	8.5 ± 6.2
- ≥8	41.7%	43.6%
Surgical risk (central eligibility committee)		
- High*	68.6%	69.9%
- Not-high	31.4%	30.1%

* STS repl score ≥8% or one or more factors present predicting extremely high surgical risk

COAPT TRIAL

Baseline Characteristics (ii)

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

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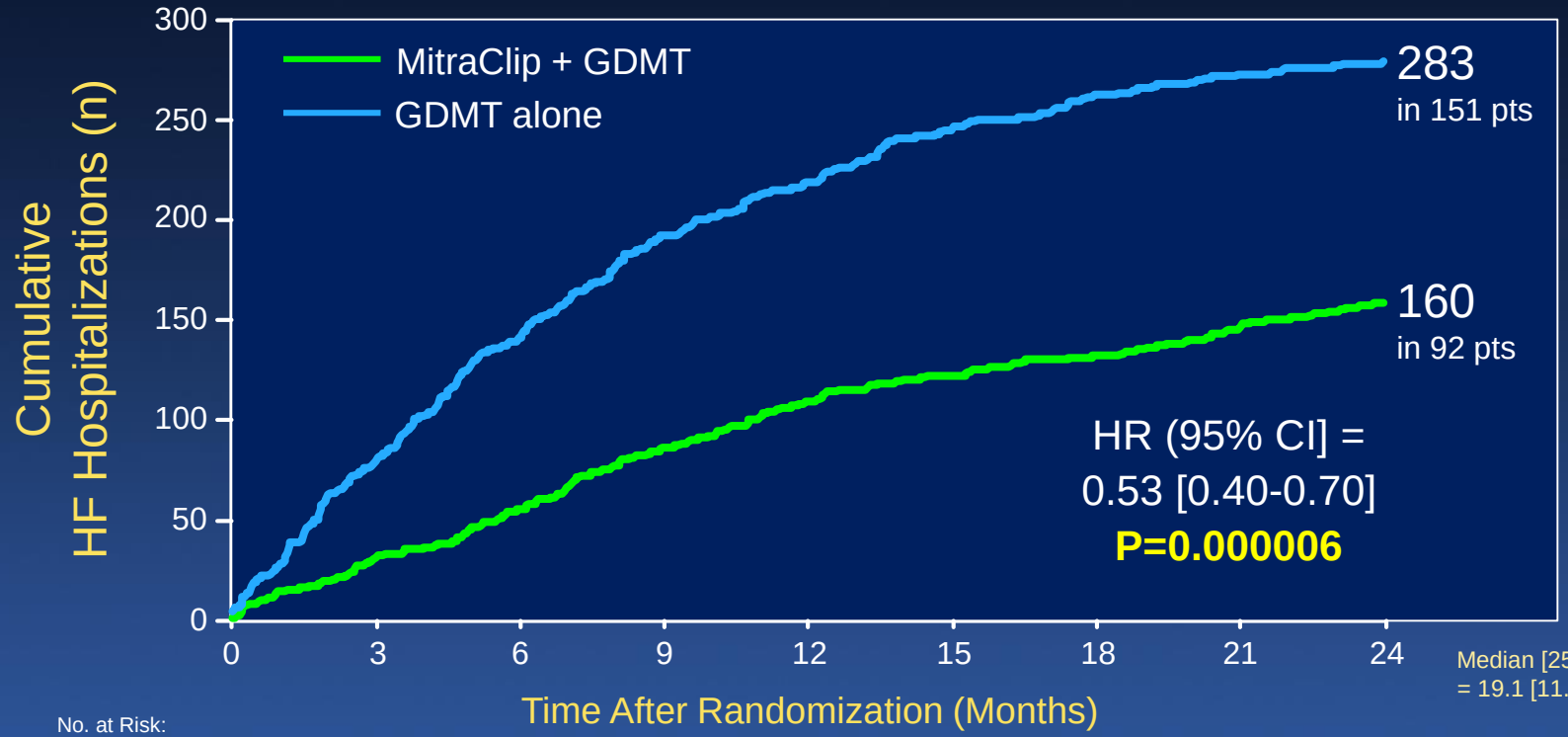
Primary Effectiveness Endpoint

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

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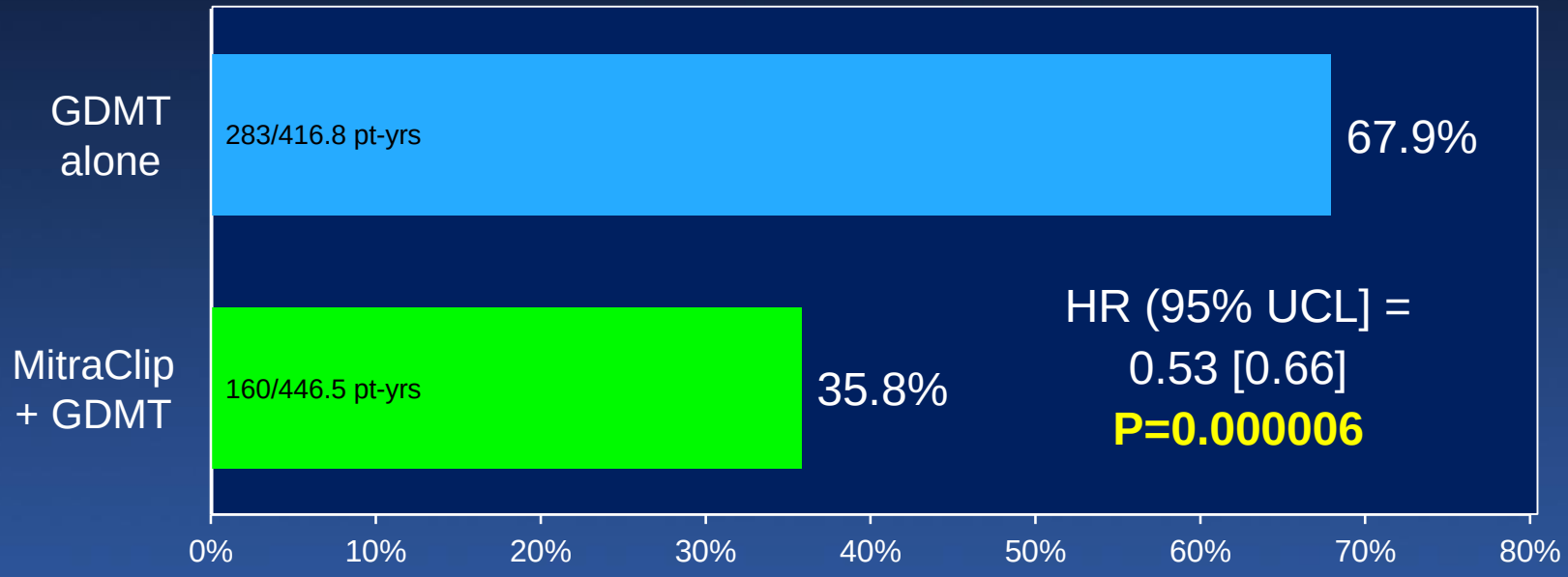
Primary Effectiveness Endpoint

Hospitalizations for HF within 24 months

Annualized rates of HF hospitalization (joint frailty model)

NNT (24 mo) = 3.1 [95% CI 1.9, 8.2]



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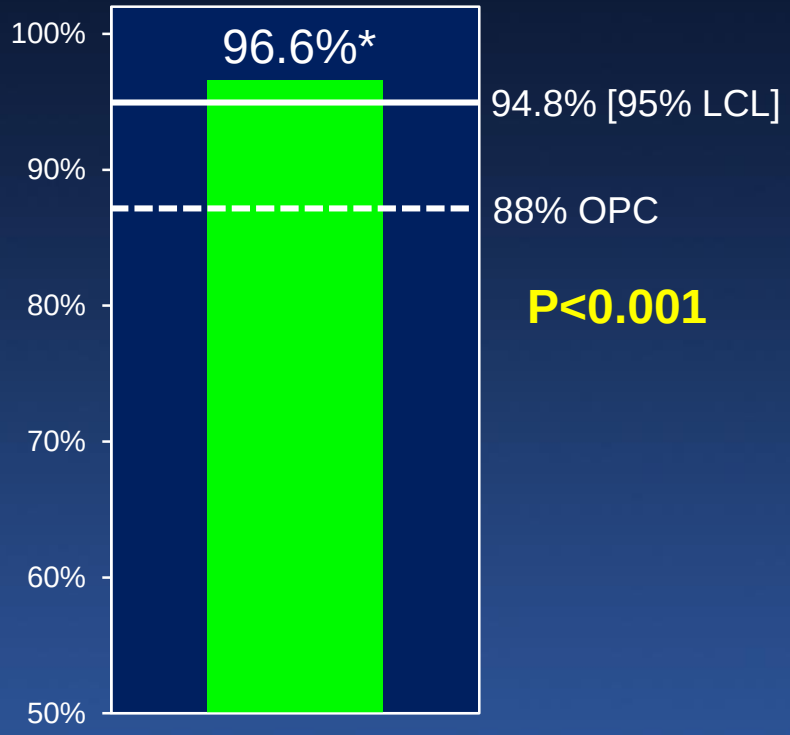
Primary Safety Endpoint

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%

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Powered Secondary Endpoints

- Tested in hierarchical order[1] -

	P-value
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)	
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

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

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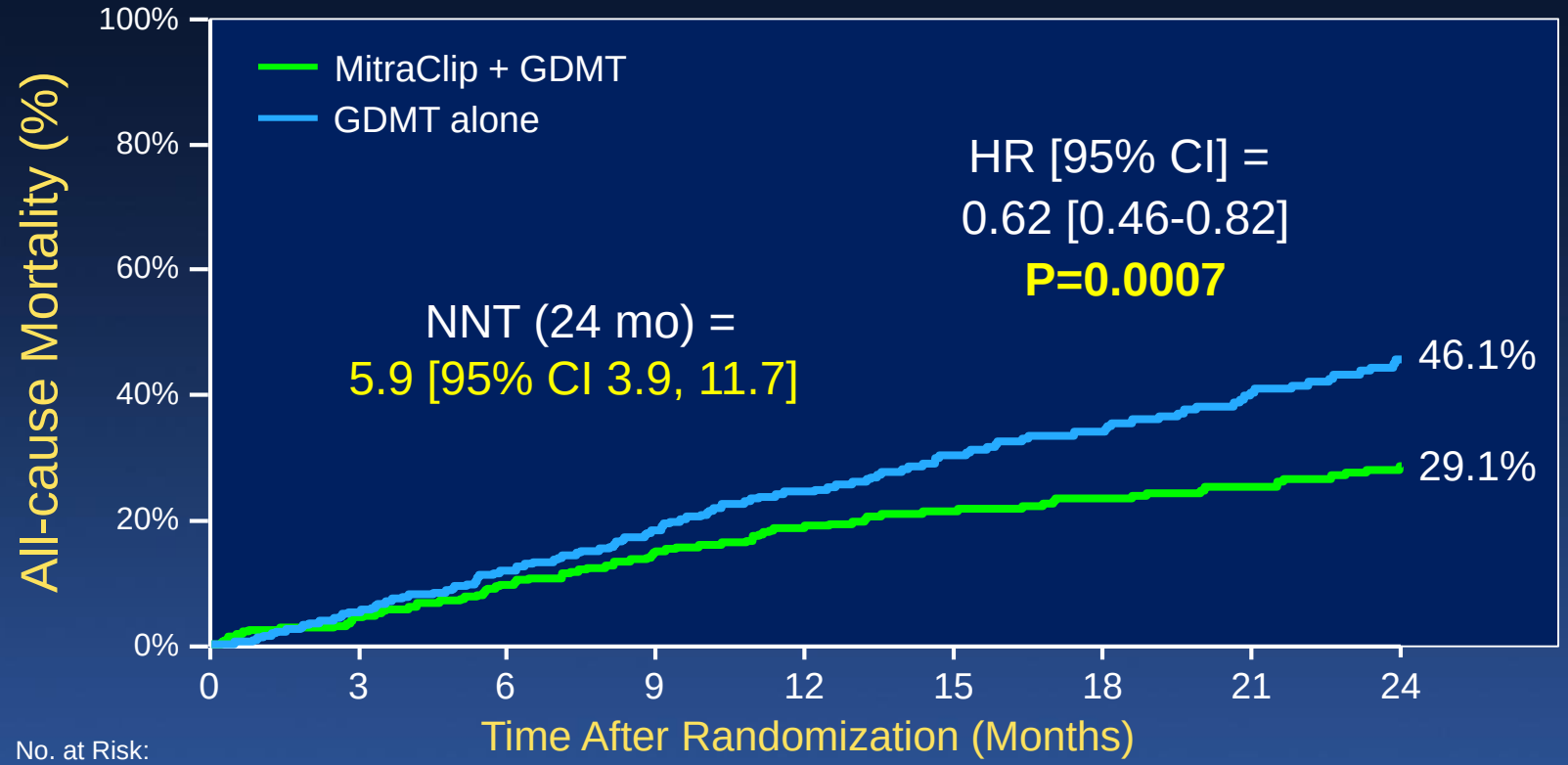
COAPT TRIAL

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

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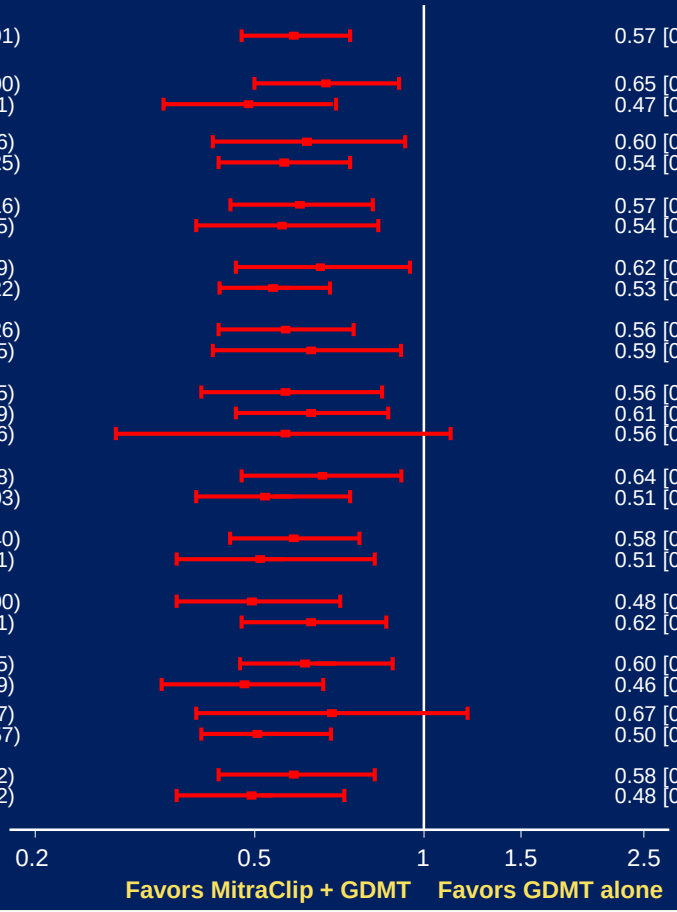
24-Month Death or HF Hospitalization

Subgroup	MitraClip + GDMT	GDMT alone	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 [0.39, 0.71]	
HF 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 MR 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 LVEF				
≥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 LVEDV (median)				
≥181 mL (n=288)	48.9% (43)	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]	



KM time-to-first event rates

*Central eligibility committee assessment

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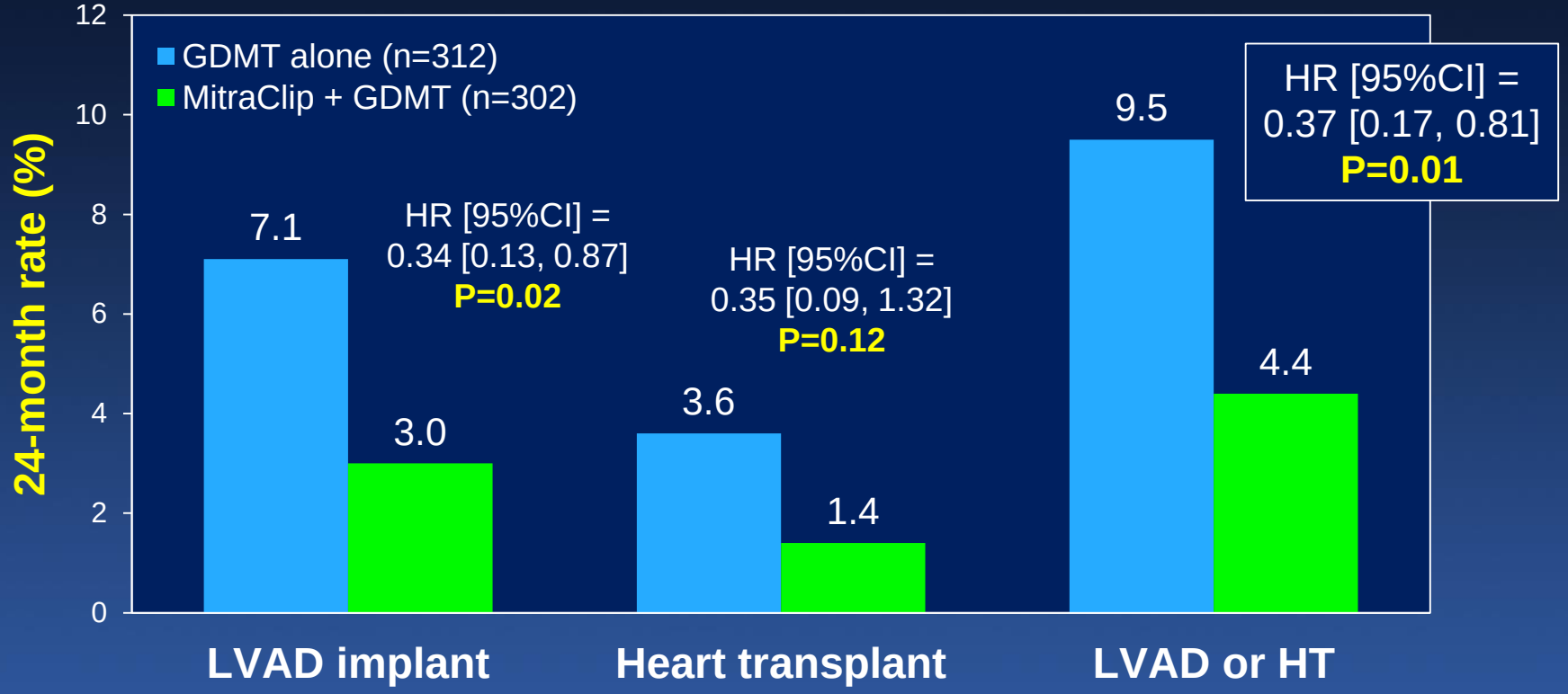
LVAD or Heart Transplant Within 24 Months



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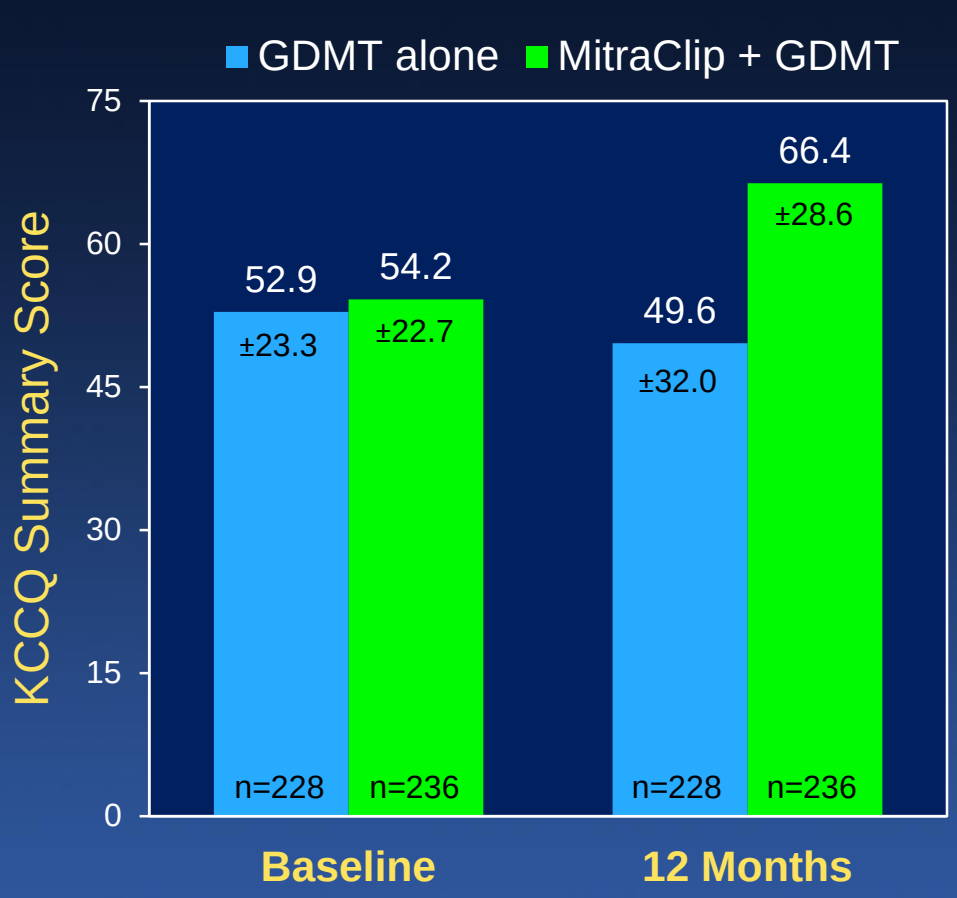
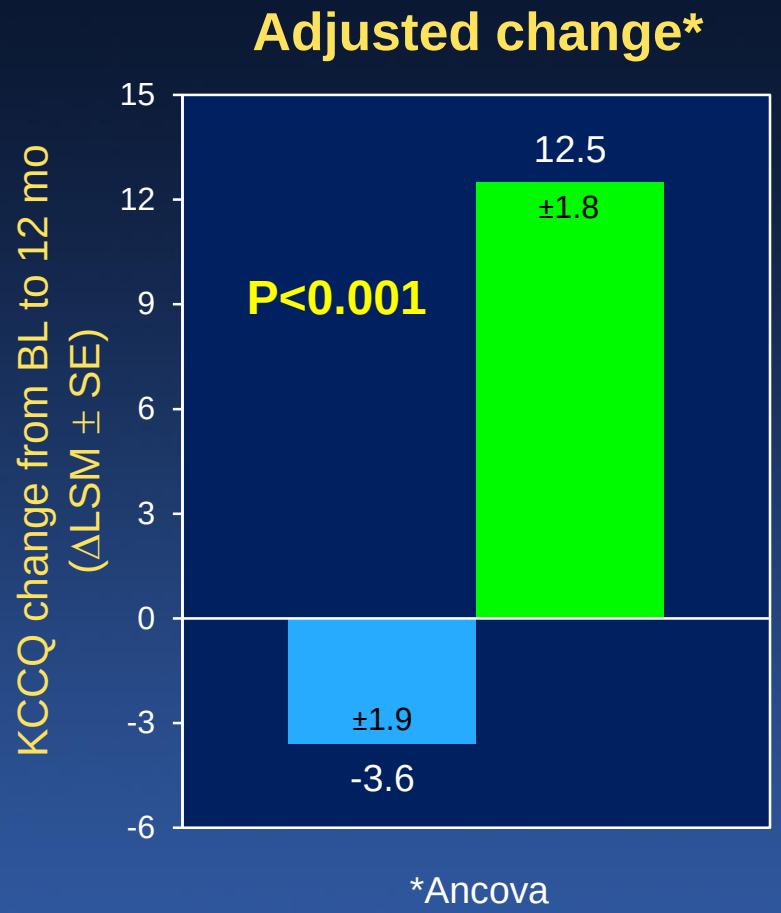
Change in KCCQ from Baseline to 12 Months





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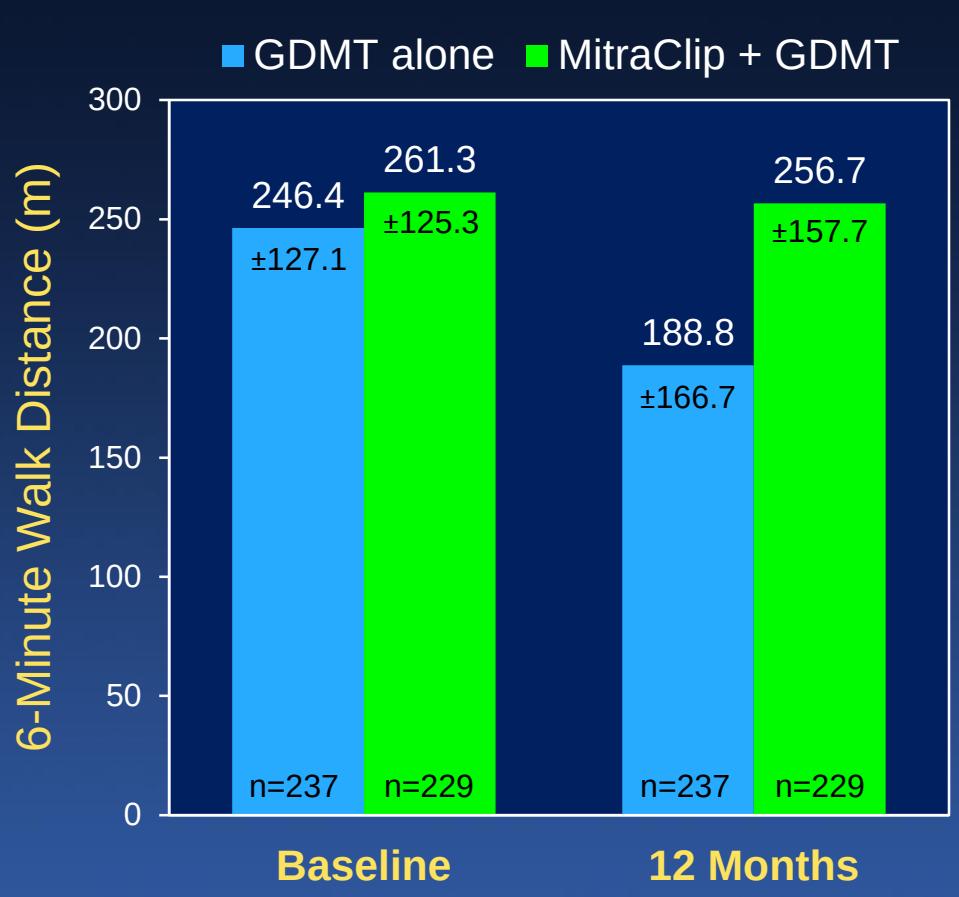
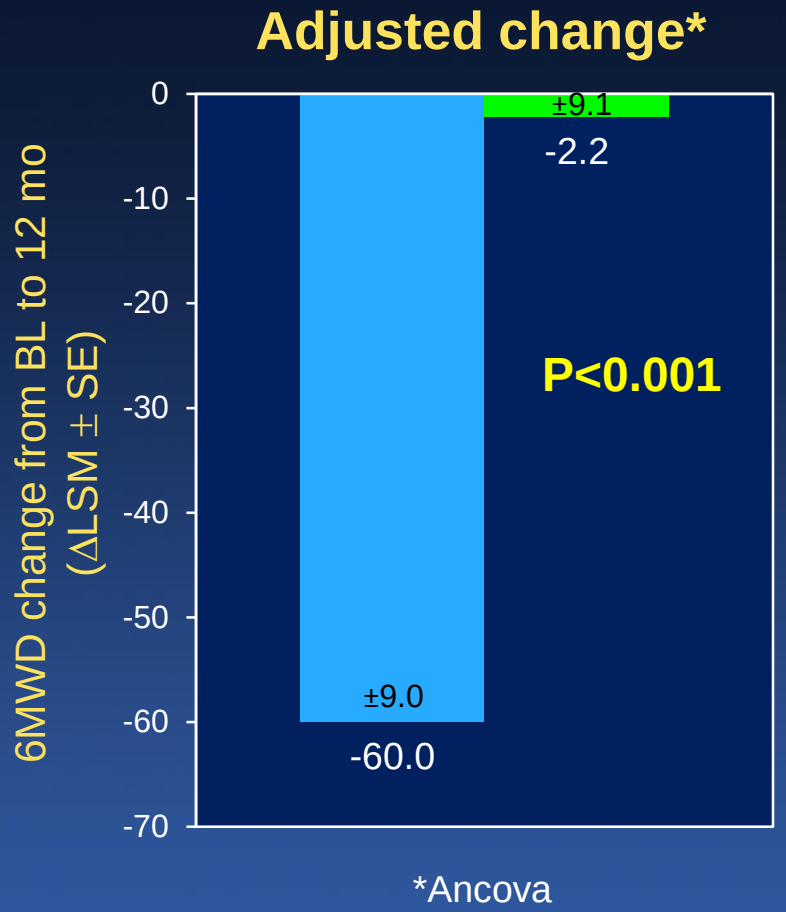
NYHA Functional Class

NYHA class	I	II	III	IV	HF death	P_{trend}	I or II	P-value
Baseline								
MitraClip (n=302)	0.3%	42.7%	51.0%	6.0%	-	-	43.0%	-
GDMT (n=311)	0%	35.4%	54.0%	10.6%	-		35.4%	
30 days								
MitraClip (n=283)	15.5%	60.8%	19.4%	3.5%	0.7%	<0.001	76.3%	<0.001
GDMT (n=281)	5.0%	42.7%	41.6%	9.6%	1.1%		47.7%	
6 months								
MitraClip (n=263)	19.4%	52.9%	21.3%	2.7%	3.8%	<0.001	72.2%	<0.001
GDMT (n=261)	5.4%	44.8%	38.3%	2.7%	8.8%		50.2%	
12 months								
MitraClip (n=237)	16.9%	55.3%	17.7%	2.5%	7.6%	<0.001	72.2%	<0.001
GDMT (n=232)	7.8%	41.8%	28.0%	4.7%	17.7%		49.6%	
24 months								
MitraClip (n=157)	12.1%	42.7%	21.7%	5.7%	17.8%	<0.001	54.8%	<0.001
GDMT (n=153)	5.2%	28.1%	23.5%	3.3%	39.3%		33.3%	

Change in 6MWD from Baseline to 12 Months





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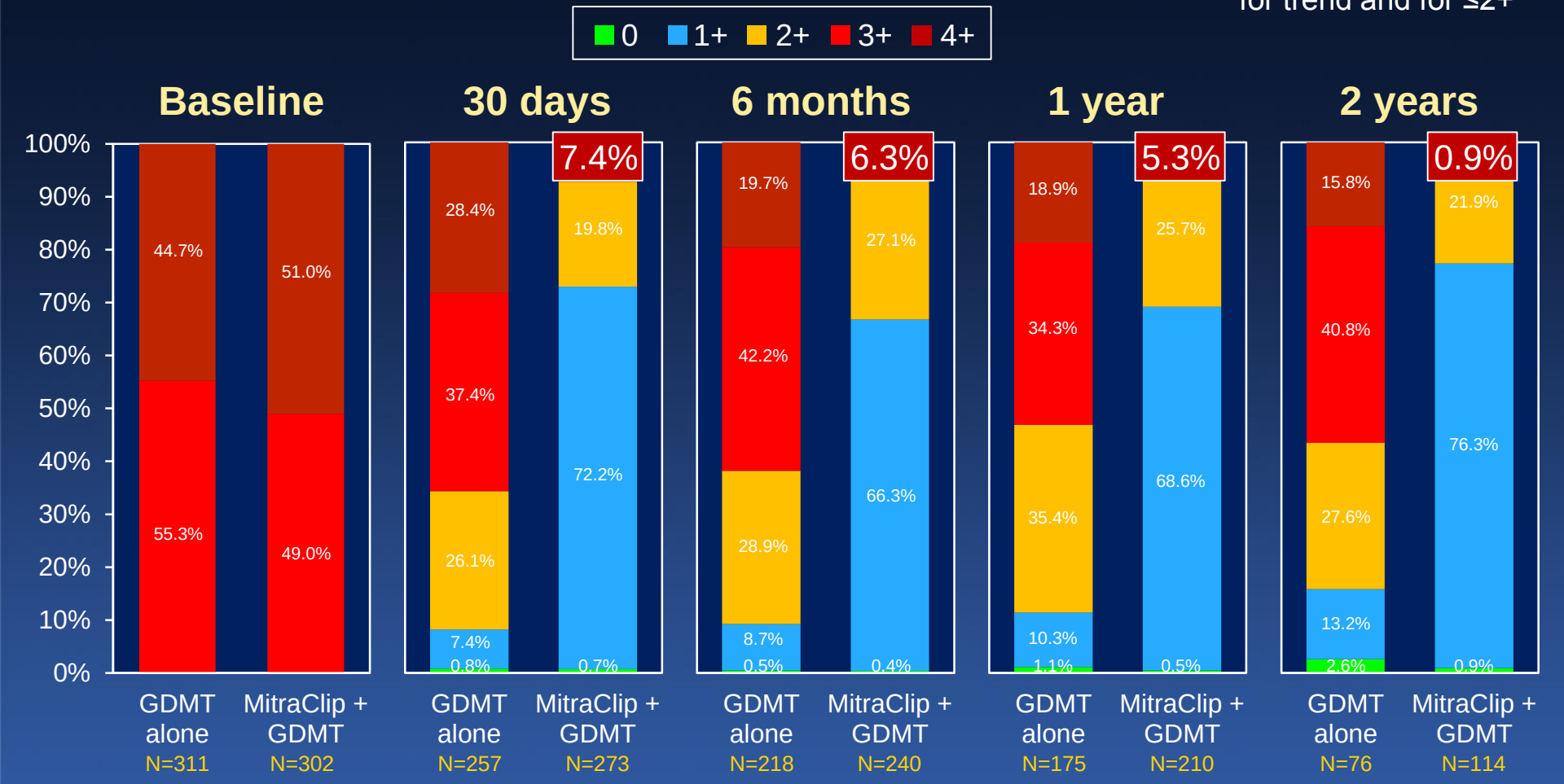
MR Severity

All FU P<0.001
for trend and for ≤2+



Predictors of 24-Month Mortality or First HF Hospitalization

Multivariable Cox regression

GDMT alone

	Hazard Ratio [95% CI]	P-Value
LVEF (%)	0.98 [0.96, 1.00]	0.027
EROA, PISA (cm^2)	3.15 [1.08, 9.21]	0.036
TR Grade (≥2+ vs ≤1+)	1.60 [1.07, 2.39]	0.022
RVSP (mmHg)	1.01 [1.00, 1.02]	0.032
STS Repl Score	1.07 [0.98, 1.18]	0.14
Age (years)	0.99 [0.97, 1.01]	0.24
STS Repair Score	0.96 [0.87, 1.07]	0.47
Isch vs Non-Isch CM	0.92 [0.62, 1.36]	0.66
LVEDV (mL)	1.00 [1.00, 1.00]	0.84
Sex (Female vs Male)	0.97 [0.64, 1.46]	0.87

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LVEDV (mL)	1.00 [1.00, 1.00]	0.84
Sex (Female vs Male)	0.97 [0.64, 1.46]	0.87

MitraClip + GDMT

	Hazard Ratio [95% CI]	P-Value
RVSP (mmHg)	1.02 [1.01, 1.04]	0.005
STS Repl Score	1.12 [1.02, 1.23]	**0.020**
LVEF (%)	1.01 [0.98, 1.03]	0.56
EROA, PISA (cm^2)	2.56 [0.79, 8.26]	0.12
TR Grade (≥2+ vs ≤1+)	0.90 [0.51, 1.61]	0.73
LVEDV (mL)	1.00 [1.00, 1.01]	0.07
Sex (Female vs Male)	0.64 [0.37, 1.08]	0.09
Isch vs Non-Isch CM	0.70 [0.43, 1.13]	0.15
STS Repair Score	0.95 [0.88, 1.04]	0.26
Age (years)	1.01 [0.98, 1.03]	0.57

Multiparametric Echo MR Assessment

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

Tier 1

EROA ≥ 0.3 cm^2

or

PV systolic flow reversal

N=570 (85.7%)

Tier 2

EROA 0.2 cm^2 - <0.3 cm^2

With any 1 of the following:

- RV ≥ 45 ml/beat
- RF ≥ 40%
- VC width ≥ 0.5 cm

N=70 (10.5%)

Tier 3

EROA not measured or <0.2 cm^2

With at least 2 of the following:

- RV ≥ 45 ml/beat
- RF ≥ 40%
- VC width ≥ 0.5 cm
- PISA radius > 0.9 cm, but CW of MR jet not done
- 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

Asch F. ACC 2019

Implications of the COAPT Trial

- In pts meeting COAPT eligibility criteria, the MitraClip should be considered the new standard of care

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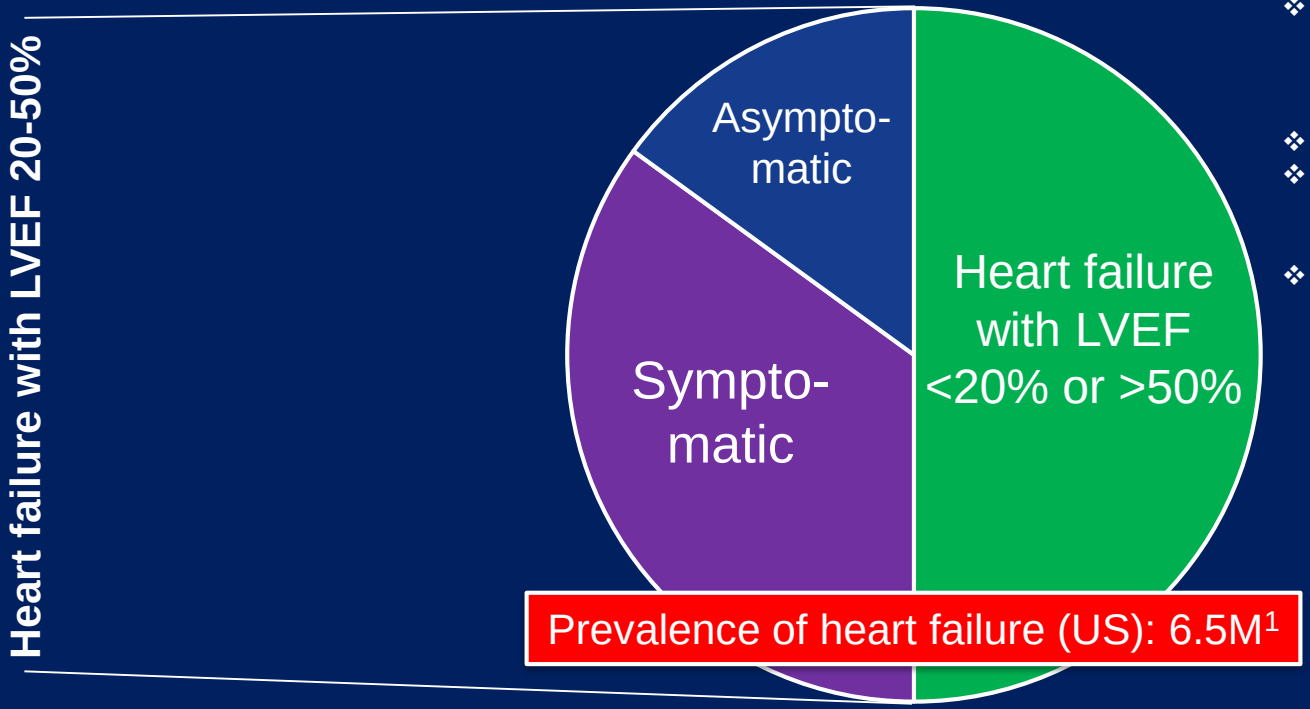


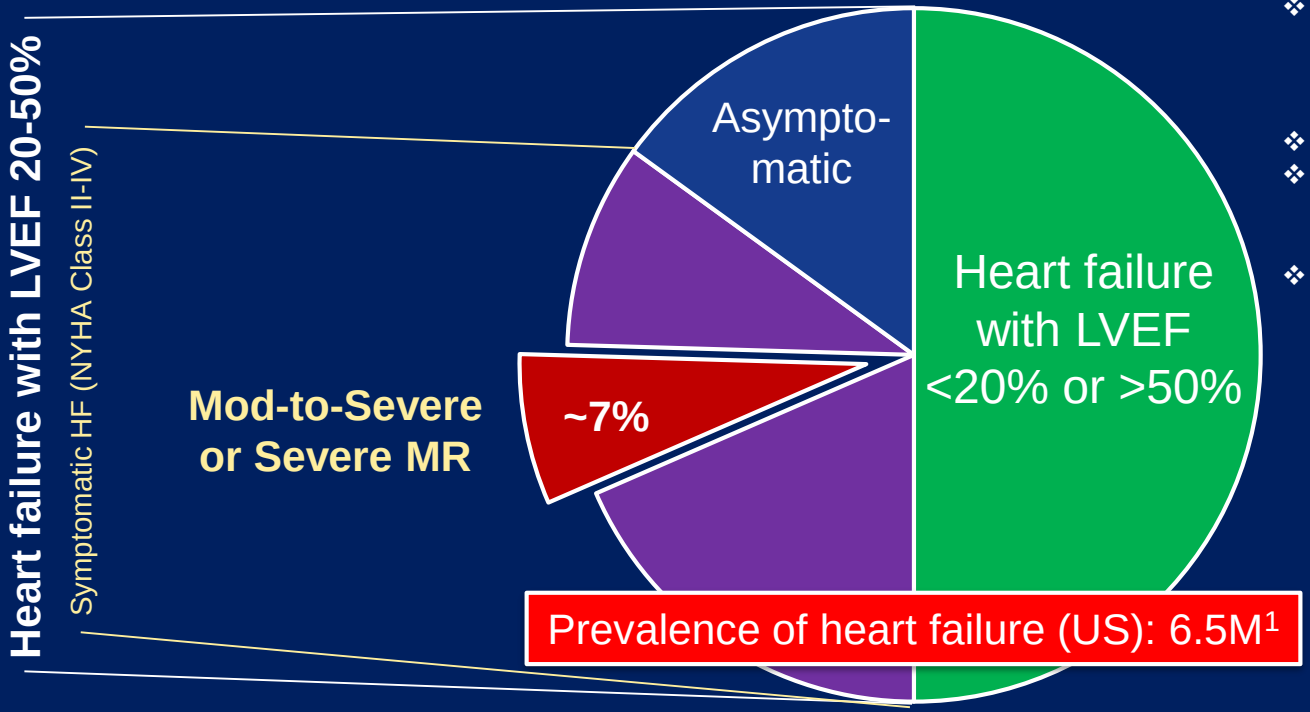
Assumptions

- LVEF 20-50%: 50% of HF
  - LVEF <40%: 50% of HF[2]
  - Assume incidence of LVEF < 20% and 40-50% are the same
- Symptomatic NYHA II-IV: ~70%
- Within symptomatic NYHA II-IV[3-5]
  - Moderate-to-severe/Severe MR: 20%
- Within Mod/Sev MR
  - Symptomatic despite GDMT: ~70%[6]
  - Anatomic suitability: ~75%

[1]AHA Heart Disease and Stroke Statistics Update, Circulation 2017
[2]Yancy CW et al, JACC 2013;
[3]Patel et al. JCF 2011
[4]Cioffi et al. EJHF 2005
[5]Goliasch et al. EHJ 2018
[6]Approximately 30% of patients in GDMT arm of COAPT improved to 2+ at 30 days

Implications of the COAPT Trial

- In pts meeting COAPT eligibility criteria, the MitraClip should be considered the new standard of care



Assumptions

- LVEF 20-50%: 50% of HF
  - LVEF <40%: 50% of HF[2]
  - Assume incidence of LVEF < 20% and 40-50% are the same
- Symptomatic NYHA II-IV: ~70%
- Within symptomatic NYHA II-IV[3-5]
  - Moderate-to-severe/Severe MR: 20%
- Within Mod/Sev MR
  - Symptomatic despite GDMT: ~70%[6]
  - Anatomic suitability: ~75%

[1]AHA Heart Disease and Stroke Statistics Update, Circulation 2017
[2]Yancy CW et al, JACC 2013;
[3]Patel et al. JCF 2011
[4]Cioffi et al. EJHF 2005
[5]Goliasch et al. EHJ 2018
[6]Approximately 30% of patients in GDMT arm of COAPT improved to 2+ at 30 days

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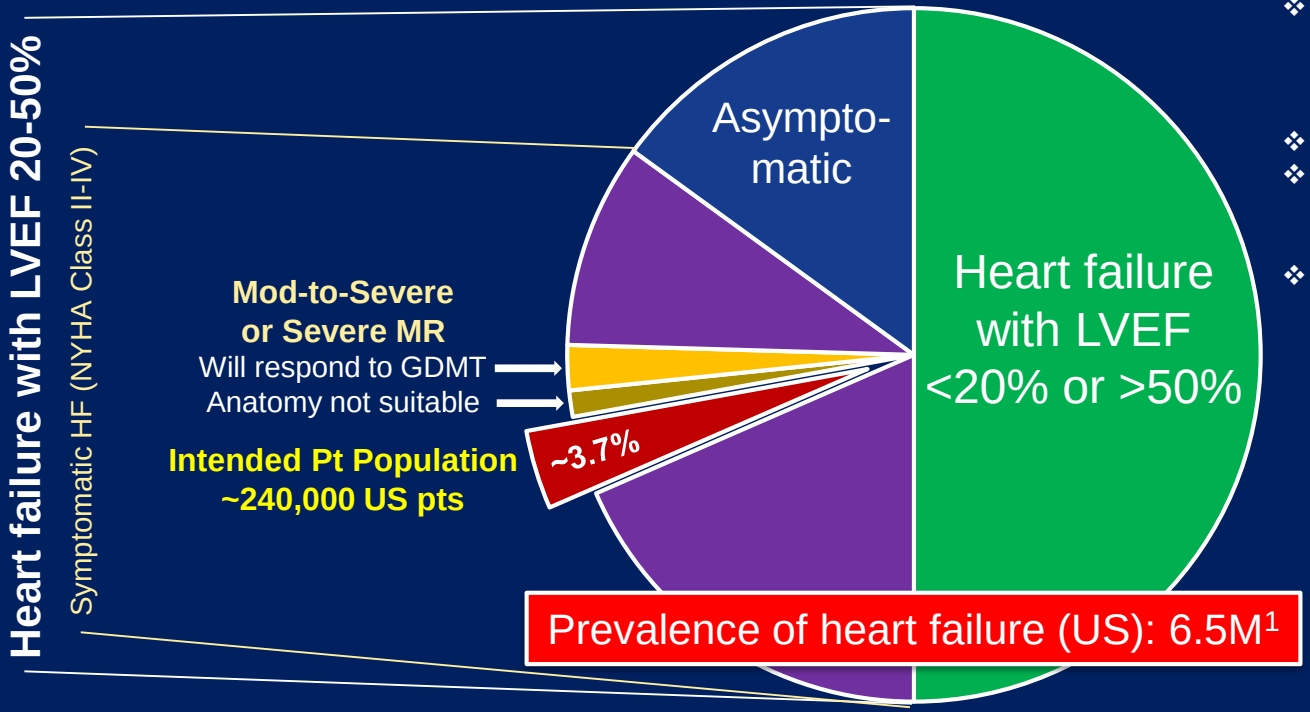

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Implications of the COAPT Trial

- In pts meeting COAPT eligibility criteria, the MitraClip should be considered the new standard of care
- However, prior to referral for the MitraClip, pts need to be given a chance to improve on all HF-GDMT, including maximally tolerated doses of ACEI/ARB/ARNI, beta-blockers, MRA, ± hydralazine/nitrates, CRT and revascularization if appropriate, and still be symptomatic with true 3+-4+ MR
- Ongoing and future trials investigating surgical and transcatheter MV repair and replacement techniques and devices in HF pts with secondary MR who meet these criteria must include the MitraClip as an active control arm