COAPT TRIAL

# COAPT

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

**Gregg W. Stone, MD**

On behalf of Michael Mack, William Abraham, JoAnn Lindenfeld and the COAPT Investigators

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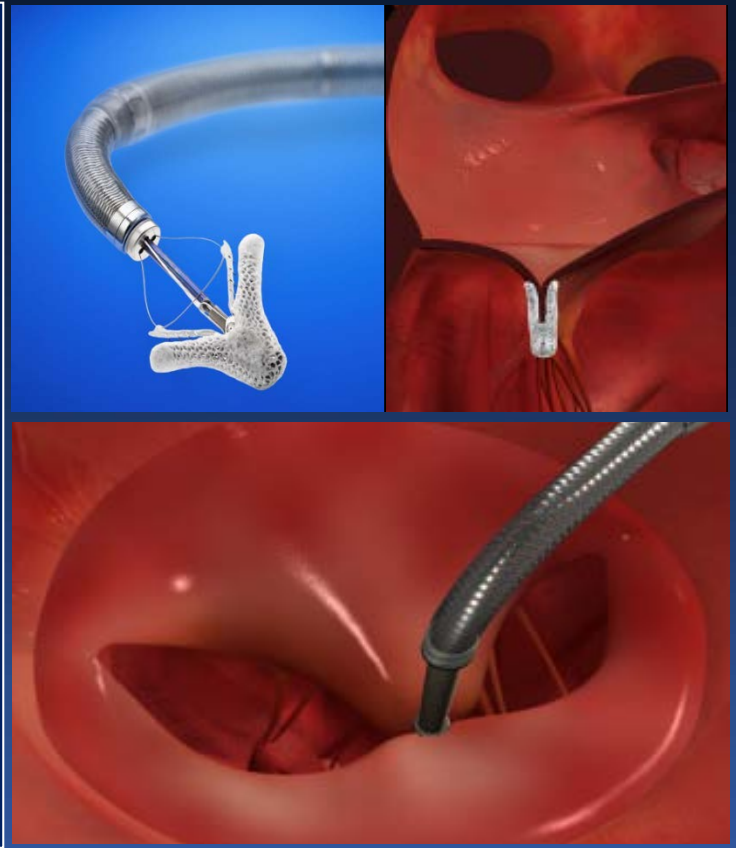
# Background (i)

- 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)

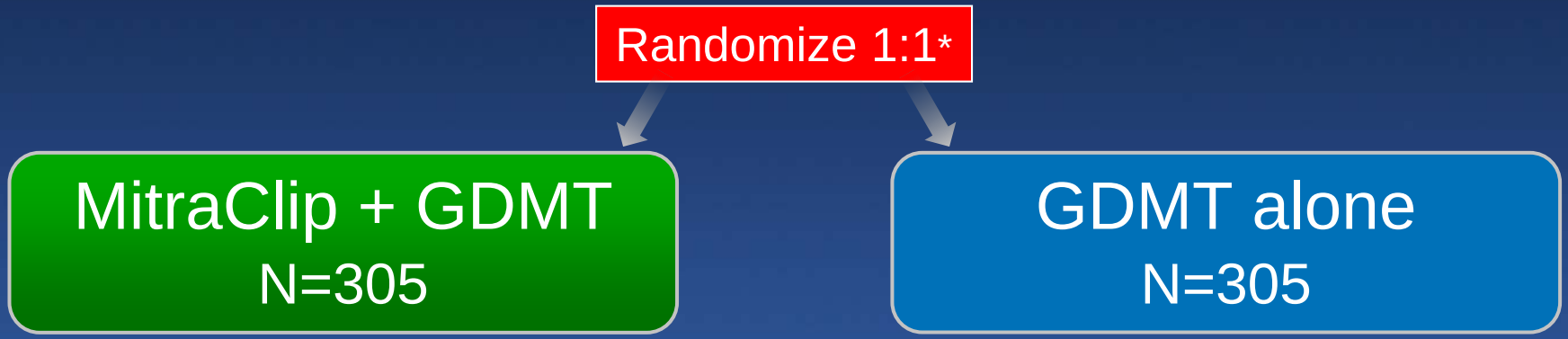
- By approximating the anterior and posterior mitral leaflets and forming a double-orifice valve, the MitraClip device reduces MR
- Registries have suggested that the MitraClip is safe and may provide symptomatic benefit to HF pts with secondary MR
- We therefore performed the COAPT randomized trial 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 ~610 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$^2$

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# Key Exclusion Criteria

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

# 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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# Baseline and Follow-up Tests

1. Clinical: Bl, 1 wk[1], 1 mo, 6 mo, 12 mo, 18 mo, 2 yrs, 3 yrs, 4 yrs, 5 yrs
2. Labs[2]: Bl, d/c[1], 1 mo, 6 mo, 12 mo, 18 mo, 2 yrs
3. TEE: Bl
4. TTE: Bl, d/c*, 1 mo, 6 mo, 12 mo, 18 mo, 2 yrs, 3 yrs, 4 yrs, 5 yrs
5. NYHA[3]: Bl, 1 mo, 6 mo, 12 mo, 18 mo, 2 yrs, 3 yrs, 4 yrs, 5 yrs
6. QOL (KCCQ and SF-36)[3]: Bl, 6 mo, 12 mo, 2 yrs
7. 6MWT[3]: Bl, 6 mo, 12 mo, 2 yrs

[1]Device group; [2]Includes BNP or NT-proBNP; [3]By blinded study personnel. Bl = baseline; d/c = discharge

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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

# 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

# Powered Secondary Endpoints

- Tested in hierarchical order[1] -

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

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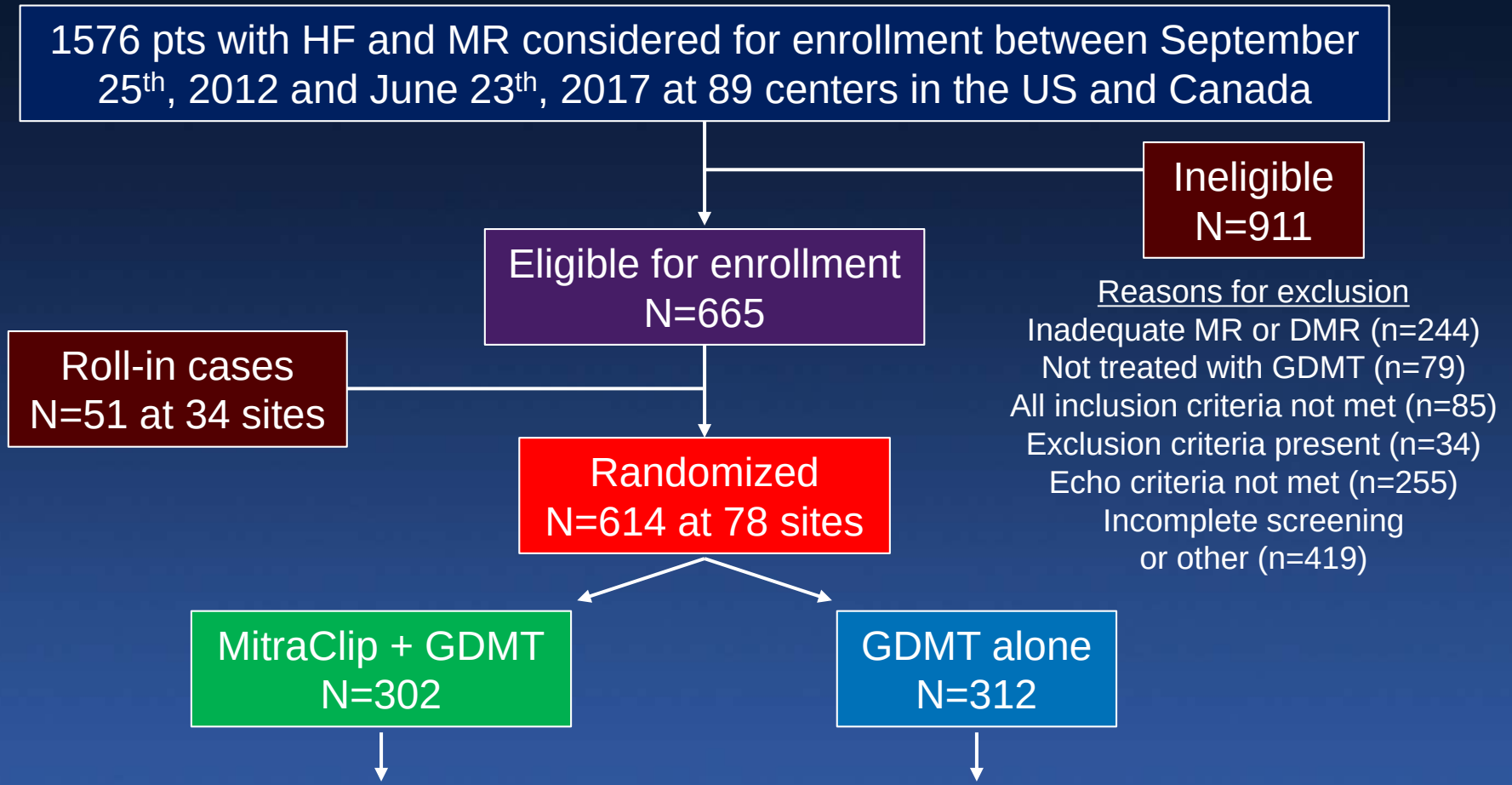
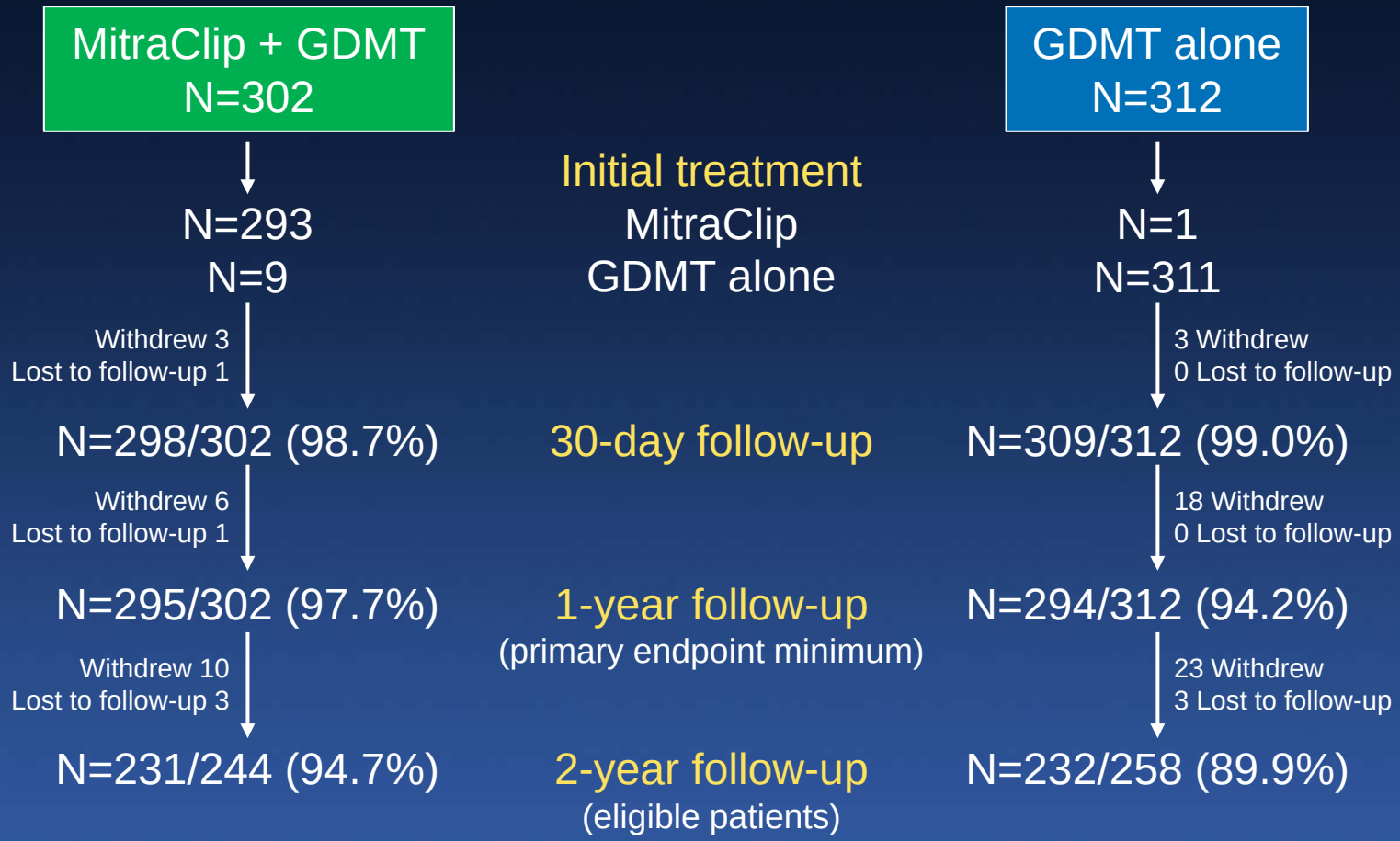
# Study Leadership

- Principal Investigators
  - Michael J. Mack, MD, Baylor Scott & White Heart Hospital Plano, Plano, TX
  - Gregg W. Stone, MD, Columbia University Medical Center, NY, NY
- Heart Failure Co-Principal Investigators
  - William T. Abraham, MD, Ohio State University, Columbus, OH
  - JoAnn Lindenfeld, MD, Vanderbilt Heart and Vascular Institute, Nashville, TN
- Steering Committee
  - Gregg W. Stone, Michael J. Mack, JoAnn Lindenfeld, William T. Abraham, Steven F. Bolling, Ted E. Feldman, Paul A. Grayburn, Samir R. Kapadia, Patrick M. McCarthy
- Central Eligibility Committee
  - Gregg Stone, Paul Grayburn, Scott Lim, Michael Zile, James Udelson, William Abraham, JoAnn Lindenfeld, Rakesh Suri, James Gammie, Marc Gillinov, Steve Bolling, Patrick McCarthy, Donald Glower, David Heimansohn
- Clinical Events Committee
  - Cardiovascular Research Foundation, New York, NY; Steven O. Marx, MD, chair
- Echocardiographic Core Laboratory
  - MedStar Health Research Institute, Hyattsville, MD; Neil J. Weissman, MD, director
- Cost-effectiveness and quality-of-life assessment
  - Saint Luke’s Mid America Heart Institute, KC, MO; David J. Cohen, MD, director
- Sponsor
  - Abbott, Santa Clara, CA

# Study Flow and Follow-up



# Study Flow and Follow-up



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# Top 10 Enrolling Sites

| | | |
|---|---|---|
| 1. Saibal Kar | Cedars-Sinai Medical Center, Los Angeles, CA | n=46 |
| 2. Scott Lim | University of Virginia, Charlottesville, VA | n=30 |
| 3. Jacob Mishell | Kaiser Permanente, San Francisco, CA | n=29 |
| 4. Brian Whisenant | Intermountain Medical Center, Murray, UT | n=26 |
| 5. Paul Grayburn | Baylor Heart and Vascular Hospital, Dallas, TX | n=25 |
| 6. Andreas Brieke | University Of Colorado Hospital, Aurora, CO | n=17 |
| 6. Michael Rinaldi | Carolinas Medical Center, Charlotte, NC | n=17 |
| 6. Samir Kapadia | Cleveland Clinic, Cleveland, OH | n=17 |
| 6. Ian Sarembock | The Christ Hospital, Cincinnati, OH | n=17 |
| 6. Vivek Rajagopal | Piedmont Hospital, Atlanta, GA | n=17 |

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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

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# 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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# Medication Use at Baseline

| | MitraClip + GDMT (n=302) | GDMT alone (n=312) |
|---|---|---|
| Beta-blocker | 91.1% | 89.7% |
| ACEI, ARB or ARNI | 71.5% | 62.8% |
| Mineralocorticoid receptor antagonist | 50.7% | 49.7% |
| Nitrates | 6.3% | 8.0% |
| Hydralazine | 16.6% | 17.6% |
| Diuretic | 89.4% | 88.8% |
| Chronic oral anticoagulant | 46.4% | 40.1% |
| Aspirin | 57.6% | 64.7% |
| P2Y12 receptor inhibitor | 25.2% | 22.8% |
| Statin | 62.6% | 60.6% |

# Major Changes in HF Meds w/i 12 Months

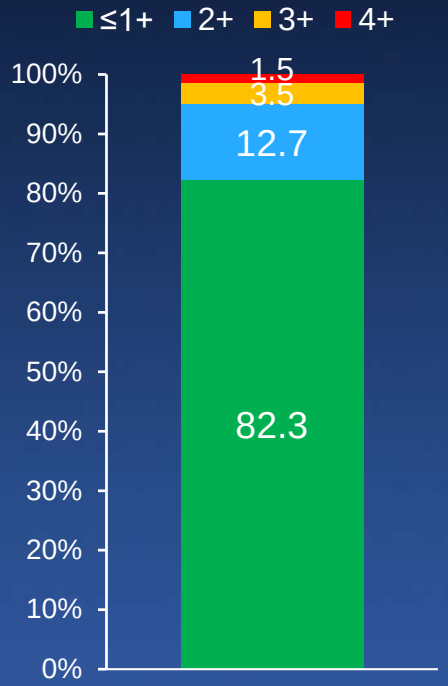
| | MitraClip + GDMT (n=302) | GDMT alone (n=312) | P value |
|---|---|---|---|
| ACEI, ARB or ARNI | | | |
| - ⇓ dose by >50% or discontinue | 6.6% | 4.8% | 0.33 |
| - ⇑ dose by >100% or new drug started | 7.6% | 7.4% | 0.91 |
| Beta-blocker | | | |
| - ⇓ dose by >50% or discontinue | 5.3% | 5.1% | 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 |

# MitraClip Procedure (n=302)

| | |
|---|---|
| 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 |

**TTE at discharge (n=260)**

**MR grade**



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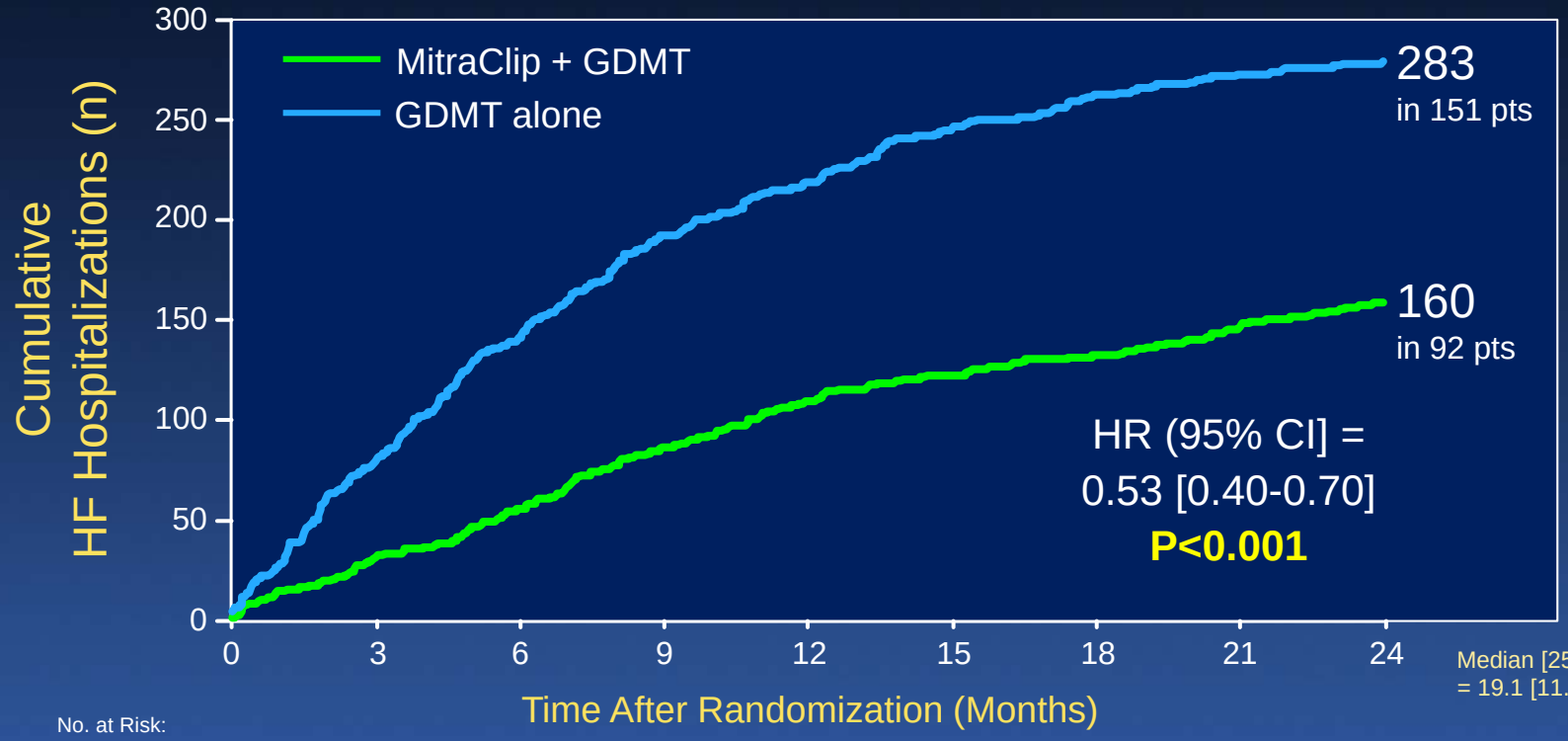
# Primary Effectiveness Endpoint

## All Hospitalizations for HF within 24 months




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

No. at Risk:

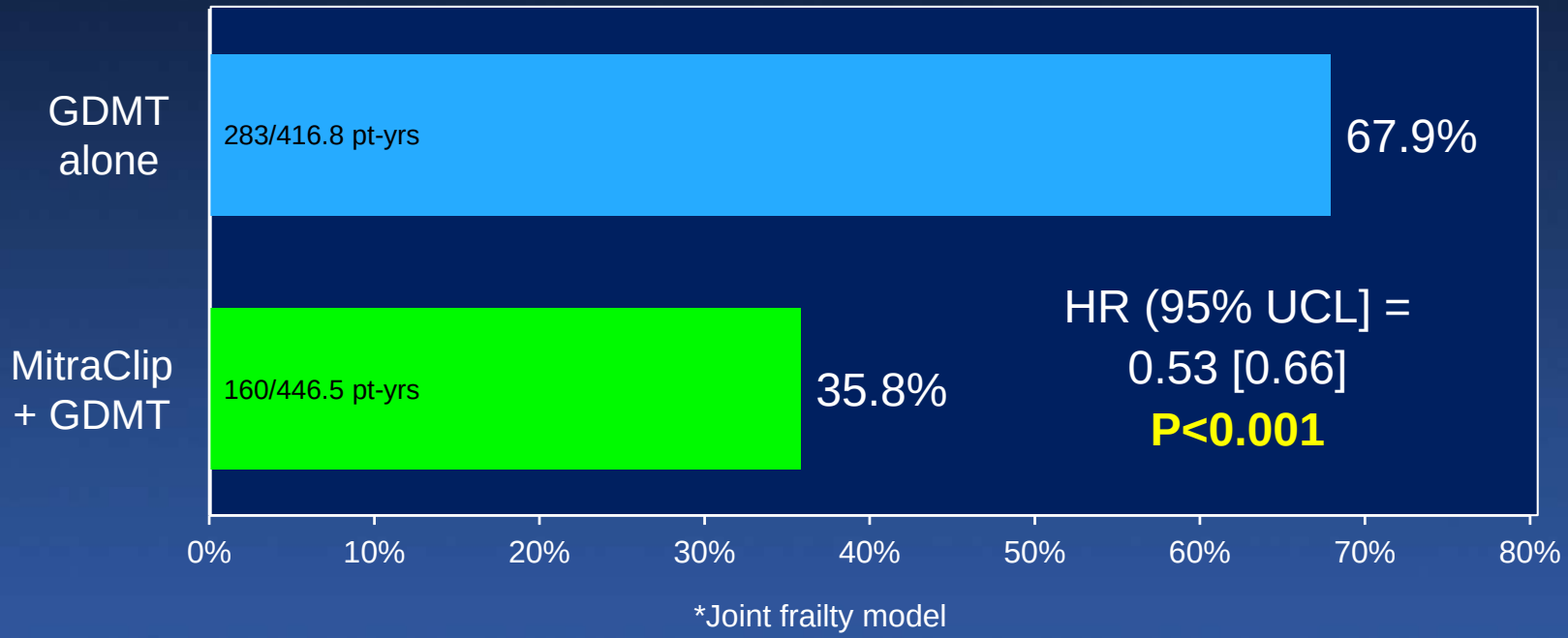
| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| MitraClip | 302 | 286 | 269 | 253 | 236 | 191 | 178 | 161 | 124 |
| GDMT | 312 | 294 | 271 | 245 | 219 | 176 | 145 | 121 | 88 |

# Primary Effectiveness Endpoint

## Hospitalizations for HF within 24 months

**Annualized rates of HF hospitalization***

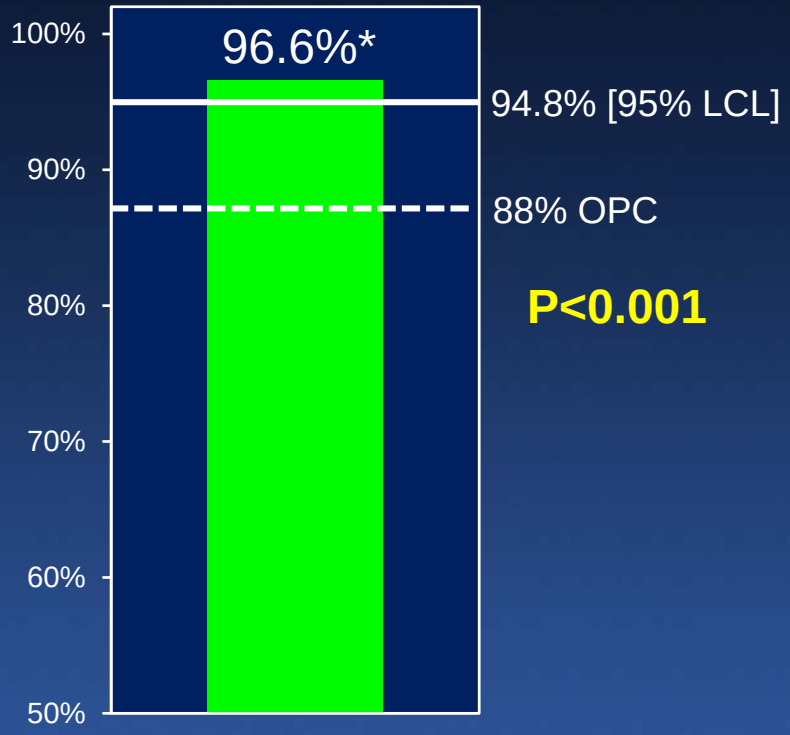
**NNT (24 mo) = 3.1 [95% CI 1.9, 8.2]**




*Joint frailty model

# 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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# Primary Endpoints

| Primary effectiveness endpoint – All HF hospitalizations through 24 months | | | | |
|---|---|---|---|---|
| **Population** | MitraClip + GDMT | GDMT alone | HR [upper 95% CL] | P-value |
| Intention-to-treat* | 35.8% (160/446.5)[1] | 67.9% (283/416.8)[1] | 0.53 [0.66] | <0.001[2] |
| As-treated | 34.8% (154/442.0)[1] | 70.6% (277/392.2)[1] | 0.44 [0.56] | <0.001[2] |
| Per-protocol | 35.4% (145/409.4)[1] | 70.0% (257/366.9)[1] | 0.45 [0.58] | <0.001[2] |
| **Primary safety endpoint – Freedom from device-related complications at 12 months** | | | | |
| **Population** | MitraClip + GDMT | GDMT alone | Lower 95% CL | P-value |
| Safety analysis* | 96.6% (9)[3] | - | 94.8% | <0.001[4] |
| As-treated | 97.5% (7)[3] | - | 95.9% | <0.001[4] |
| Per-protocol | 97.7% (6)[3] | - | 96.1% | <0.001[4] |

The intention-to-treat population consists of all pts randomized in the trial, analyzed in the group randomized, regardless of the treatment actually received. The as-treated population consists of all randomized pts according to the treatment they received. Pts who experience a death or HF hospitalization prior to a MitraClip procedure are considered to be in the Control group regardless of their initial randomization. Pts who experience a death or HF hospitalization after (but not prior to) a MitraClip procedure are considered to be in the MitraClip group regardless of their initial randomization. For pts who do not experience a death or HF hospitalization at any time during follow-up, they will be assigned to the group that constituted >50% of their follow-up duration. The per-protocol population consists of all randomized pts who meet all major study inclusion criteria and none of the major exclusion criteria for the trial, are treated according to the randomized assignment, and followed consistent with all major study processes. Pts who are randomized to the Device group but do not have a MitraClip procedure attempted between 1-14 days of the randomization are excluded from the per-protocol population. For pts in the Control group who receive the MitraClip device, follow-up data after the date of the procedure will be excluded from analysis. For subjects in either group who undergo other major intervention for HF (e.g. mitral valve surgery, LVAD implant or heart transplant), follow-up data after the date of the intervention will be excluded from analysis. The safety analysis population consists of all randomized Device group subjects in whom a MitraClip procedure is attempted.[1]Annualized event rate (total number of events/patient-years of follow-up); [2]Joint frailty model; [3]Kaplan-Meier time-to-first event estimates (number of events); [4]Calculated from Z test with Greenwood's method of estimated variance against a pre-specified performance goal of 88%. *Population for the study primary endpoint.

# 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

# 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

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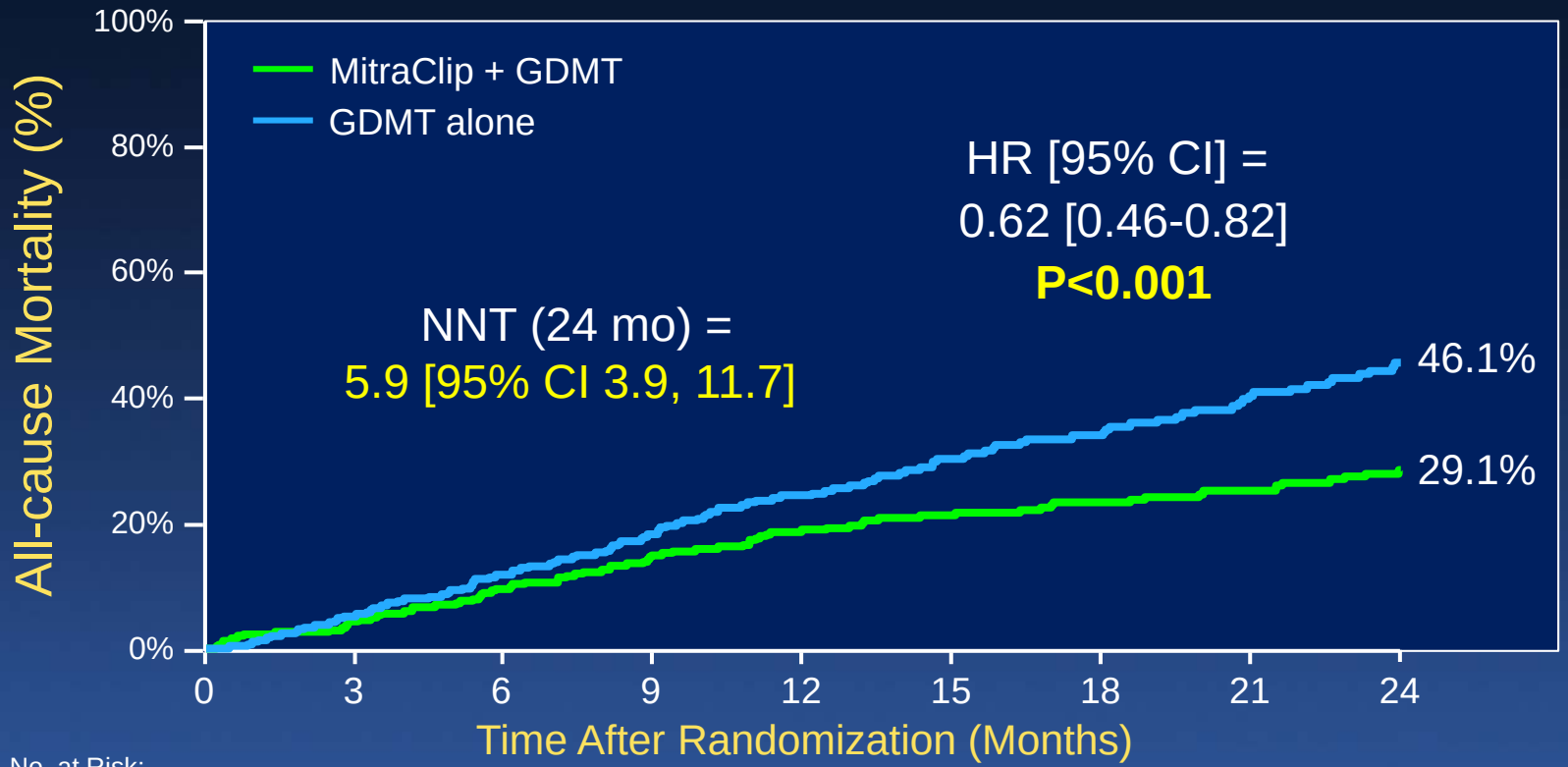
# All-cause Mortality




| 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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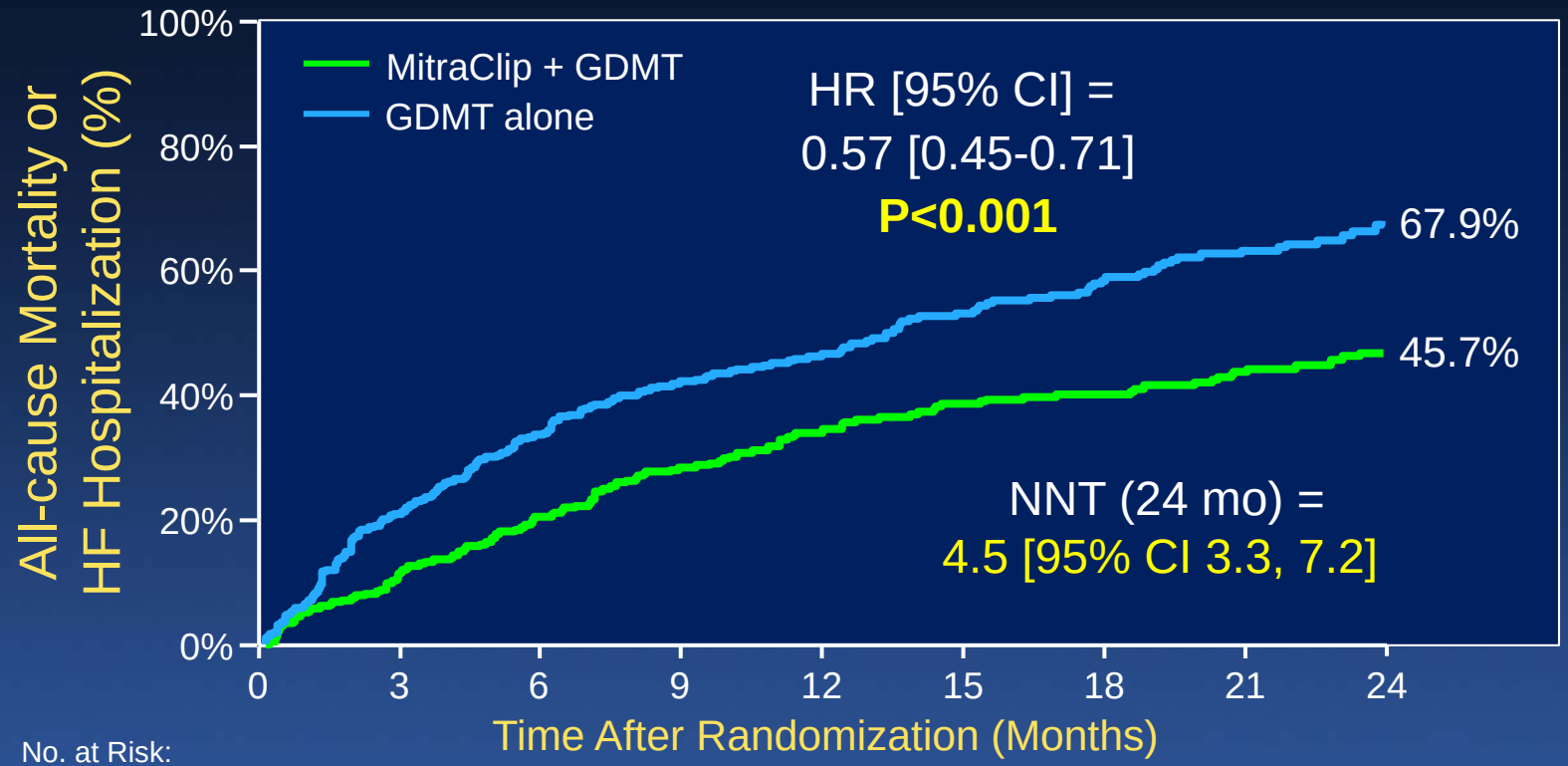
# Death or HF Hospitalization




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 |

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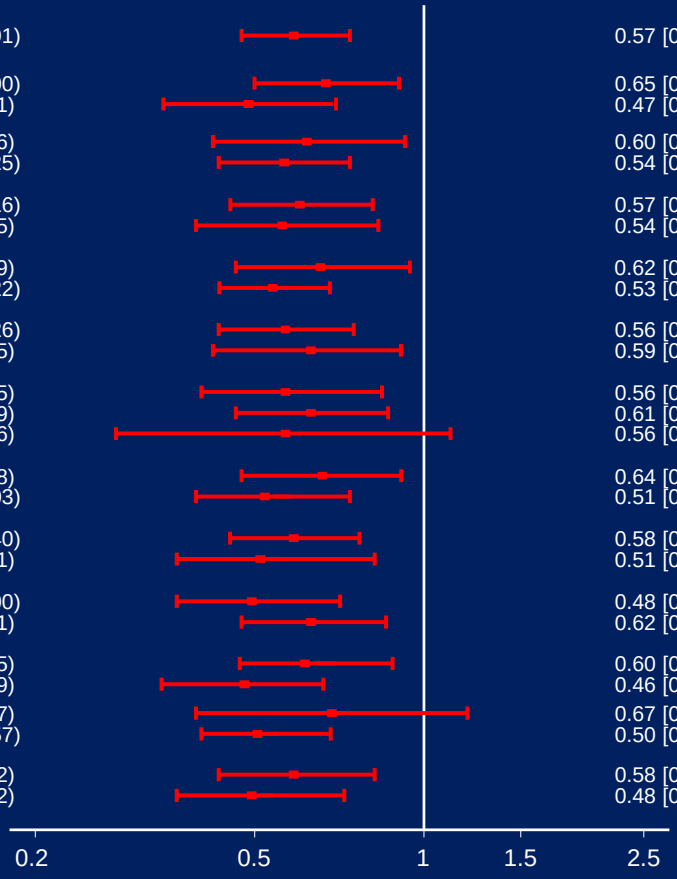
# 24-Month Death or HF Hospitalization

| 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

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

# 24-Month Event Rates (ii)

| | 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 |

*Unplanned. Kaplan-Meier time-to-first event rates

COAPT TRIAL

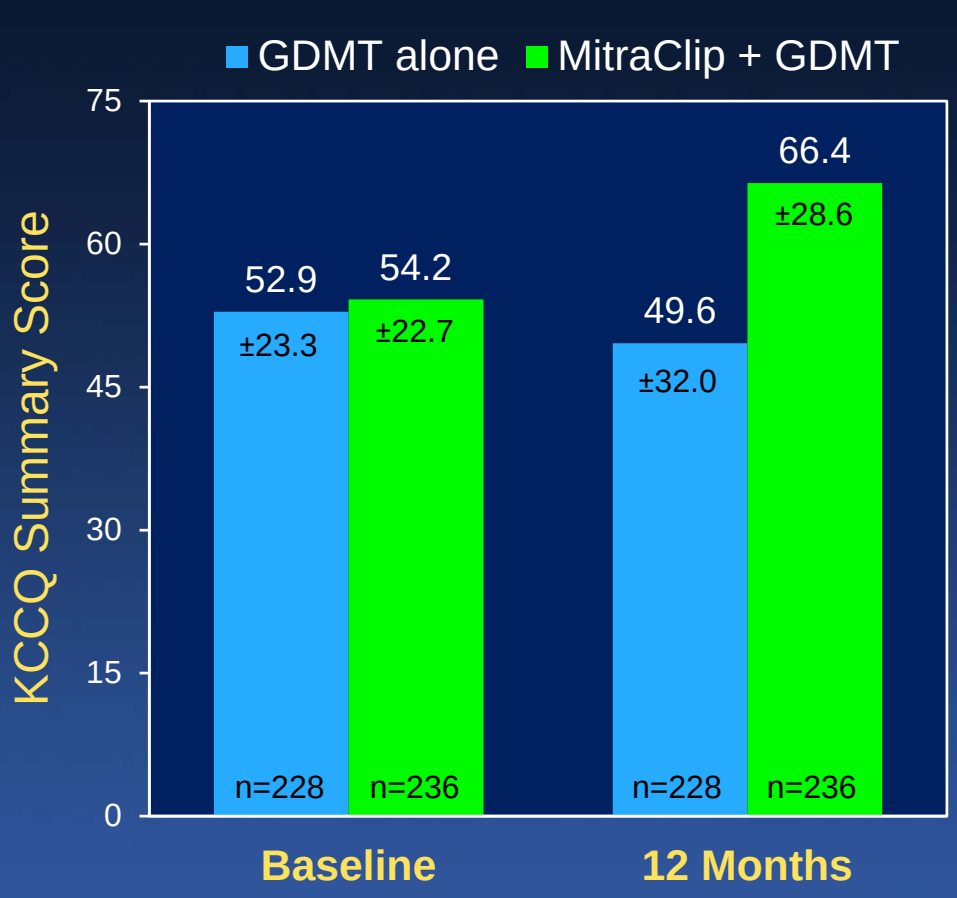
# 24-Month Event Rates (ii)

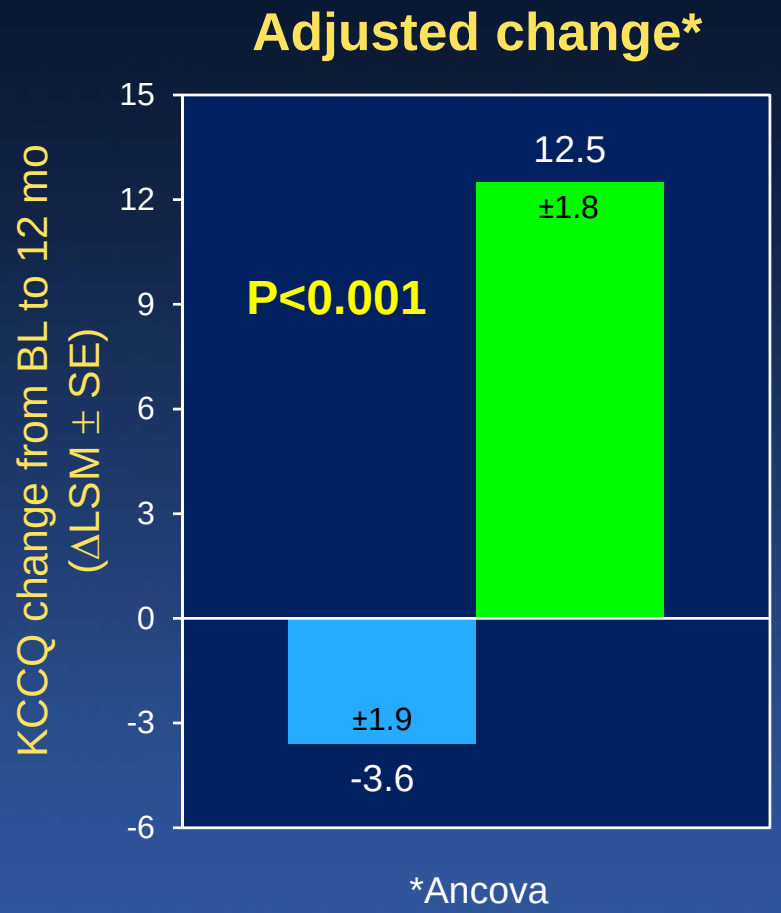
| | MitraClip + GDMT (n=302) | GDMT alone (n=312) | HR [95% CI] | P-value |
|---|---|---|---|---|
| MV intervention or surgery* | 4.0% | 9.0% | 0.61 [0.27, 1.36] | 0.23 |
| - MitraClip | 3.7% | 6.6% | 0.99 [0.38, 2.58] | 0.99 |
| - Mitral valve surgery | 0.4% | 2.5% | 0.14 [0.02, 1.17] | 0.07 |
| PCI 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 |

*Unplanned. Kaplan-Meier time-to-first event rates

COAPT TRIAL

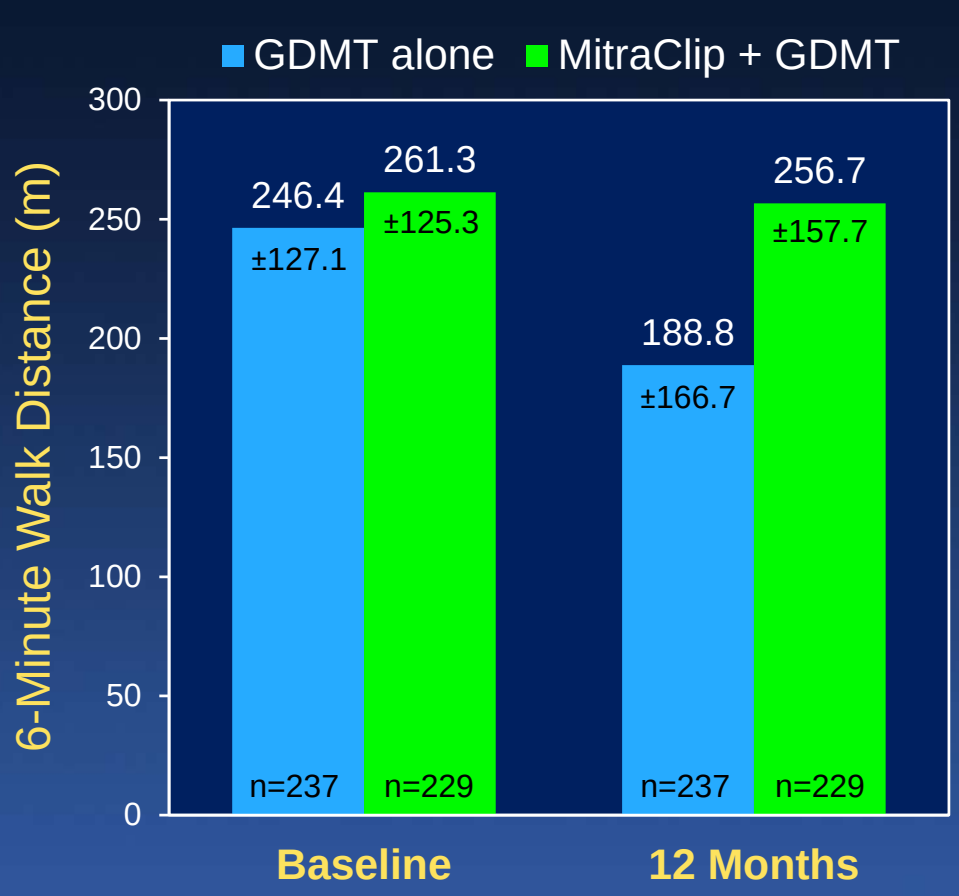
# Change in KCCQ from Baseline to 12 Months

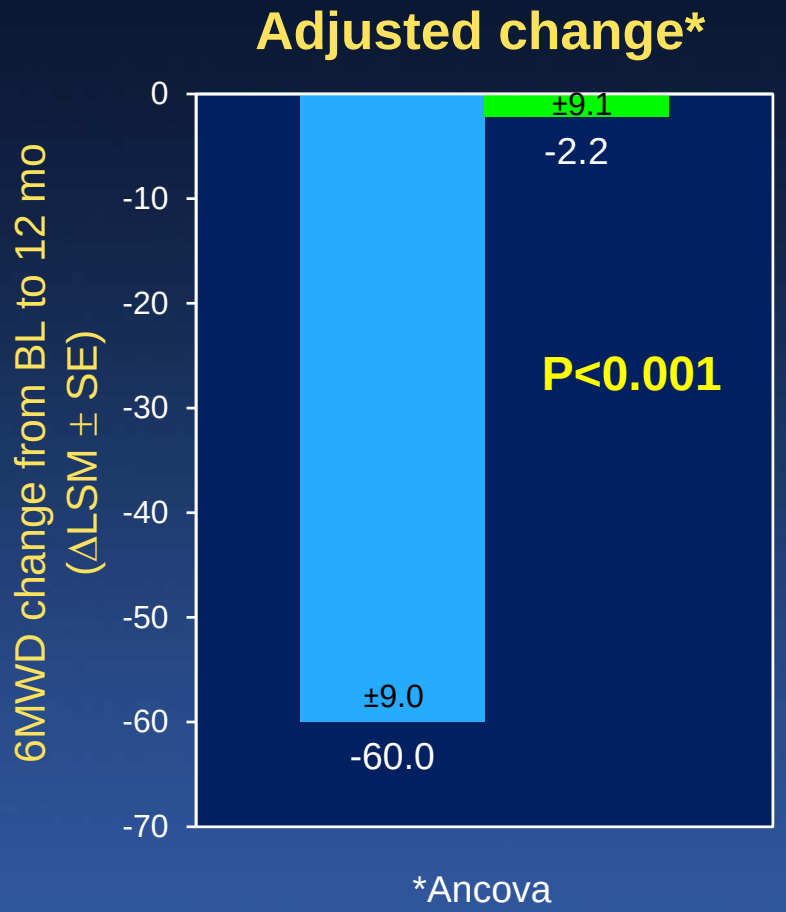



*Ancova

# Change in 6MWD from Baseline to 12 Months



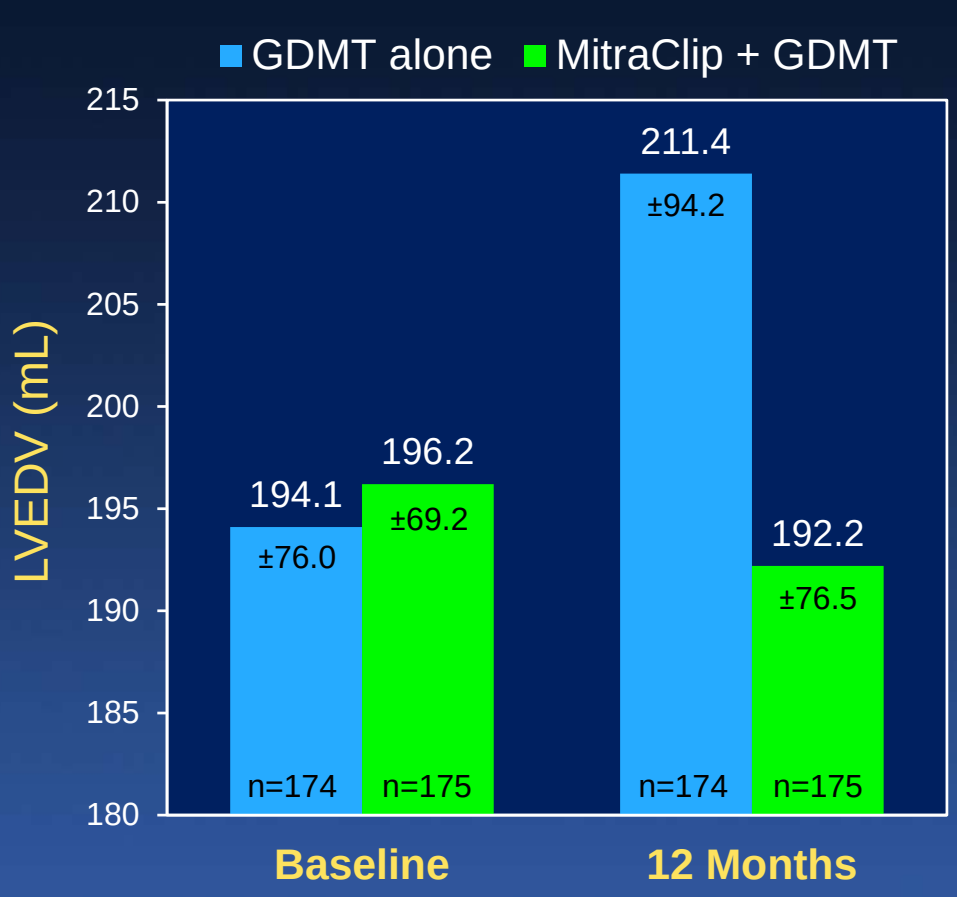



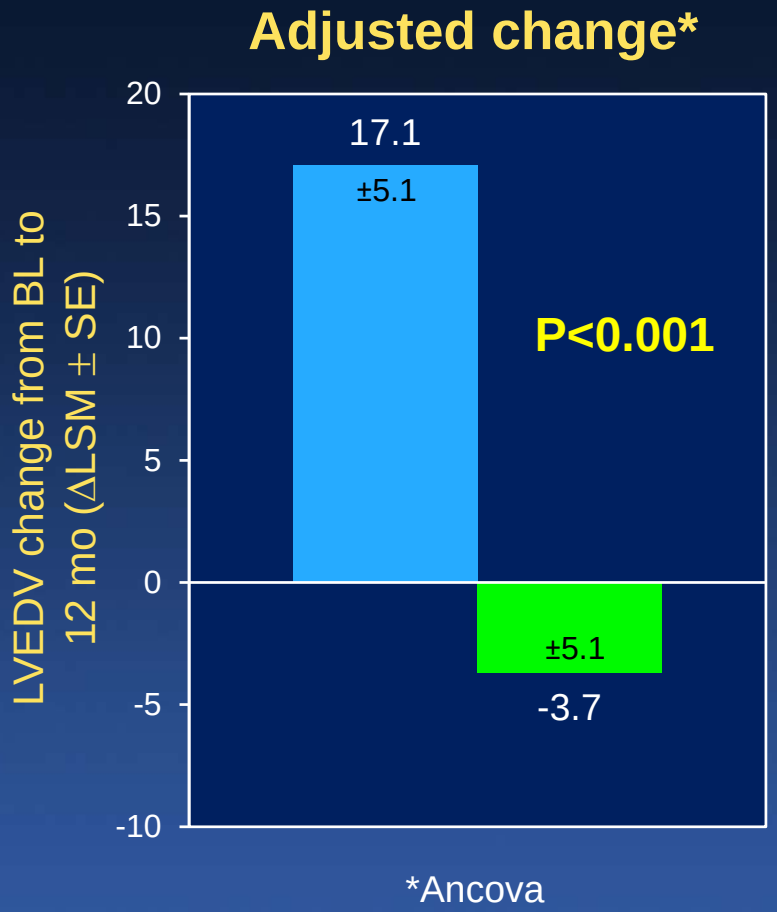
COAPT TRIAL

# 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 LVEDV from Baseline to 12 Months



COAPT TRIAL

# MR Severity (Core Lab)

| MR grade | ≤1+ | 2+ | 3+ | 4+ | $P_{trend}$ | ≤2+ | P-value |
|---|---|---|---|---|---|---|---|
| Baseline | | | | | | | |
| MitraClip (n=302) | - | - | 49.0% | 51.0% | - | - | - |
| GDMT (n=311) | - | - | 55.3% | 44.7% | | - | |
| 30 days | | | | | | | |
| MitraClip (n=273) | 72.9% | 19.8% | 5.9% | 1.5% | <0.001 | 92.7% | <0.001 |
| GDMT (n=257) | 8.2% | 26.1% | 37.4% | 28.4% | | 34.2% | |
| 6 months | | | | | | | |
| MitraClip (n=240) | 66.7% | 27.1% | 4.6% | 1.7% | <0.001 | 93.8% | <0.001 |
| GDMT (n=218) | 9.2% | 28.9% | 42.2% | 19.7% | | 38.1% | |
| 12 months | | | | | | | |
| MitraClip (n=210) | 69.1% | 25.7% | 4.3% | 1.0% | <0.001 | 94.8% | <0.001 |
| GDMT (n=175) | 11.4% | 35.4% | 34.3% | 18.9% | | 46.9% | |
| 24 months | | | | | | | |
| MitraClip (n=114) | 77.2% | 21.9% | 0% | 0.9% | <0.001 | 99.1% | <0.001 |
| GDMT (n=76) | 15.8% | 27.6% | 40.8% | 15.8% | | 43.4% | |

# MR Severity (Core Lab)

| MR grade | ≤1+ | 2+ | 3+ | 4+ | $P_{trend}$ | ≤2+ | P-value |
|---|---|---|---|---|---|---|---|
| Baseline | | | | | | | |
| MitraClip (n=302) | - | - | 49.0% | 51.0% | - | - | - |
| GDMT (n=311) | - | - | 55.3% | 44.7% | | - | |
| 30 days | | | | | | | |
| MitraClip (n=273) | 72.9% | 19.8% | 5.9% | 1.5% | <0.001 | 92.7% | <0.001 |
| GDMT (n=257) | 8.2% | 26.1% | 37.4% | 28.4% | | 34.2% | |
| 6 months | | | | | | | |
| MitraClip (n=240) | 66.7% | 27.1% | 4.6% | 1.7% | <0.001 | 93.8% | <0.001 |
| GDMT (n=218) | 9.2% | 28.9% | 42.2% | 19.7% | | 38.1% | |
| 12 months | | | | | | | |
| MitraClip (n=210) | 69.1% | 25.7% | 4.3% | 1.0% | <0.001 | 94.8% | <0.001 |
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| 24 months | | | | | | | |
| MitraClip (n=114) | 77.2% | 21.9% | 0% | 0.9% | <0.001 | 99.1% | <0.001 |
| GDMT (n=76) | 15.8% | 27.6% | 40.8% | 15.8% | | 43.4% | |

COAPT TRIAL

# MR Severity (Core Lab)

| MR grade | ≤1+ | 2+ | 3+ | 4+ | $P_{trend}$ | ≤2+ | P-value |
|---|---|---|---|---|---|---|---|
| Baseline | | | 3+-4+ | | | | |
| MitraClip (n=302) | - | - | 49.0% | 51.0% | - | - | - |
| GDMT (n=311) | - | - | 55.3% | 44.7% | | - | |
| 30 days | | | 7.4% | | | | |
| MitraClip (n=273) | 72.9% | 19.8% | 5.9% | 1.5% | <0.001 | 92.7% | <0.001 |
| GDMT (n=257) | 8.2% | 26.1% | 37.4% | 28.4% | | 34.2% | |
| 6 months | | | 6.3% | | | | |
| MitraClip (n=240) | 66.7% | 27.1% | 4.6% | 1.7% | <0.001 | 93.8% | <0.001 |
| GDMT (n=218) | 9.2% | 28.9% | 42.2% | 19.7% | | 38.1% | |
| 12 months | | | 5.3% | | | | |
| MitraClip (n=210) | 69.1% | 25.7% | 4.3% | 1.0% | <0.001 | 94.8% | <0.001 |
| GDMT (n=175) | 11.4% | 35.4% | 34.3% | 18.9% | | 46.9% | |
| 24 months | | | 0.9% | | | | |
| MitraClip (n=114) | 77.2% | 21.9% | 0% | 0.9% | <0.001 | 99.1% | <0.001 |
| GDMT (n=76) | 15.8% | 27.6% | 40.8% | 15.8% | | 43.4% | |

COAPT TRIAL

# Limitations

- Because the MitraClip is visible on imaging tests, COAPT was unblinded
  - Bias was mitigated by GDMT standardization and use of independent CEC & ECL
- Median FU duration was greater in the Device than the Control group
  - In part due to improved survival
  - However, study withdrawals were more frequent in the Control group
  - Results were consistent using multiple imputation to account for missing data
- The present results apply to Rx of secondary MR with the MitraClip
  - Whether other transcatheter or surgical approaches would have comparable results is uncertain
- Pts were symptomatic (NYHA II - IVa) despite maximally-tolerated GDMT (with more than one-third having undergone CRT), had true moderate-to-severe or severe MR, LVEF 20%-50%, and frequent comorbidities
  - Whether the MitraClip would be as safe and effective in more or less critically ill pts or those with lesser degrees of MR severity is unknown

# Why are the COAPT Results so Different from MITRA-FR?

## Possible Reasons

| | MITRA-FR (n=304) | COAPT (n=614) |
|---|---|---|
| Severe MR entry criteria | Severe FMR by EU guidelines: EROA >20 $mm^2$ or RV >30 mL/beat | Severe FMR by US guidelines: EROA >30 $mm^2$ or RV >45 mL/beat |
| EROA (mean ± SD) | 31 ± 10 $mm^2$ | 41 ± 15 $mm^2$ |
| LVEDV (mean ± SD) | 135 ± 35 $mL/m^2$ | 101 ± 34 $mL/m^2$ |
| 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 |
| Acute results: No clip / ≥3+ MR | 9% / 9% | 5% / 5% |
| Procedural complications* | 14.6% | 8.5% |
| 12-mo MitraClip ≥3+ MR | 17% | 5% |

*MITRA-FR defn: device implant failure, transf or vasc compl req surg, ASD, card shock, cardiac embolism/stroke, tamponade, urg card surg

COAPT TRIAL

# Conclusions

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

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*