COMPREHENSIVE PREVENTION, DIAGNOSIS AND TREATMENT OF CARDIOVASCULAR DISEASE
MITRAL REGURGITATION

ORGANIC, FUNCTIONAL
AND
NEW THERAPIES
NO DISCLOSURES
Anatomy

- Mitral Annulas
- Anterior Leaflet
- Posterior Leaflet
- Chordae
- Papillary Muscles
- Left Ventricle
MITRAL VALVE DISEASE

Classifications:

- **Etiology** – cause
  - **Primary (Structural, Organic)** – valvular tissue
  - **Secondary (Functional)** – affecting supporting structure

- **Functional**

- **Carpentier**

  Based on analysis of motion of leaflets
MITRAL VALVE DISEASE

Primary Valve Diseases

- Congenital malformations
- Inflammatory diseases
- Degenerative diseases
- Bacterial endocarditis
- Calcification
- Trauma
- Tumors

Secondary Valve Diseases

- Myocardial infarction
- Dilated cardiomyopathies
- Hypertrophied cardiomyopathies
- Endomyocardial fibrosis
MITRAL REGURGITATION

Severity of MR:  ASE – consensus 2017
AHA/ACC – 2017 guidelines

- Structural
  LA size
  LV size
  MV apparatus
- Qualitative and Quantitative Doppler
  Vena contracta
  PISA
  Regurgitant volume
  Regurgitant fraction
  EROA
  Pulmonary vein flow
- Hemodynamic consequences
- Symptomatology
MITRAL REGURGITATION

Quantitative echo parameters to grade MR severity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC width (cm)</td>
<td>&lt; 0.3</td>
<td>0.3 – 0.69</td>
<td>≥ 0.7</td>
</tr>
<tr>
<td>RVol (mL/beat)</td>
<td>&lt; 30</td>
<td>30 – 44, 45 – 59</td>
<td>≥ 60</td>
</tr>
<tr>
<td>RF (%)</td>
<td>&lt; 30</td>
<td>30 – 39, 40 – 49</td>
<td>≥ 50</td>
</tr>
<tr>
<td>EROA (cm²)</td>
<td>&lt; 0.20</td>
<td>0.20 – 0.29, 0.30 – 0.39</td>
<td>≥ 0.40</td>
</tr>
</tbody>
</table>

VC = vena contracta
RVol = regurgitant volume
RF = regurgitant fraction
Prognostic Determinants

Severity
Left Ventricular Function
Symptoms
Asymptomatic DMR
Natural History

Risk Factors
- Age ≥50 yrs
- Atrial fibrillation
- LA enlargement
- Flail
- Mild MR

Survival %

Years after diagnosis

≤1 RF
95 ±2

≥2 RF
70 ±5

MR ≥3
or
EF <50%

Asymptomatic Primary MR

Severity and Survival

Worse Survival

Survival (%)

0 10 20 30 40 50 60 70 80 90 100

Years

ERO <20mm² (91 ±3%)
ERO 20-39mm² (66 ±6%)
ERO ≥40mm² (58 ±9%)

P<0.01

More CV Events

Rate of Cardiac Events %

0 10 20 30 40 50 60 70

Years

ERO ≥40mm² (62 ±8%)
ERO 20-39mm² (40 ±7%)
ERO <20mm² (15 ±4%)

P<0.01

Enriquez-Sarano M et al. NEJM 2005;352:875-83
EF and Surgical Outcome

![Graph showing survival rates for different EF categories over 10 years.]

- **EF ≥60%**: 72 ±4%
- **EF 50-60%**: 53 ±9%
- **EF <50%**: 32 ±12%

*P*=0.0001

**EF <60% is Abnormal in MR**

Enriquez-Sarano M, et al., Circulation 1994;90:830-837
Symptoms and Surgery

Outcome with Primary MR

Survival %

NYHA I-II

NYHA III-IV

Years

P<0.0001

Tribouilley CM et al., Circulation 1999;99:400-5
Flail Mitral Leaflet

Natural History

Survival %

Years After Diagnosis

Mortality

Class I or II
4% per year

Class III or IV
34% per year

P<0.001

Secondary Mitral Regurgitation

Increased Severity = Increased Morbidity


Mitral Regurgitation

Untreated severe MR is associated with increased morbidity and mortality

What about therapy?
FIGURE 2 Indications for Surgery for MR (Updated Figure 4 From the 2014 VHD guideline)
MITRAL VALVE SURGERY

Annuloplasty
MITRAL VALVE SURGERY

Triangular Resection

- Damaged segment of mitral valve
- Segment removed
- Cut edges sutured together
- Annuloplasty band

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MITRAL VALVE SURGERY

Quadrangular Resection
MITRAL VALVE SURGERY

Gortex chordal repair
MITRAL VALVE REPLACEMENT
A Largely Untreated Patient Population

Mitral Regurgitation 2009 U.S. Prevalence

Total MR Patients\textsuperscript{1,2} 4,100,000

Eligible for Treatment\textsuperscript{3,4} (MR Grade $\geq 3+$) 1,670,000

Annual Incidence\textsuperscript{3} (MR Grade $\geq 3+$) 30,000

Annual MV Surgery\textsuperscript{5} Pending

Untreated Large and Growing Clinical Unmet Need

14% Newly Diagnosed Each Year

ALTERNATIVES TO CONVENTIONAL MV SURGERY

MITRAL CLIP
Transcatheter Mitral Repair is indicated for the percutaneous reduction of significant symptomatic mitral regurgitation (MR ≥ 3+) due to primary abnormality of the mitral apparatus [degenerative MR] in patients who have been determined to be at prohibitive risk for mitral valve surgery by a heart team, which includes a cardiac surgeon experienced in mitral valve surgery and a cardiologist experienced in mitral valve disease, and in whom existing comorbidities would not preclude the expected benefit from reduction of the mitral regurgitation.
Transcatheter Mitral Repair

ACC/AHA Guidelines – Primary MR

May be considered for prohibitive risk patients with primary MR and severe symptoms despite GDMT (class IIb)
Mitral Clip Experience

- **EVEREST I** Feasibility (n=55)
- **EVEREST II** Pivotal
  - Pre-Randomization (n=60)
  - HR Registry (n= 78)
  - Randomized (2:1 Clip to Surgery) (n= 279)
- **REALISM** Registry
  - Continued Access (n=965)
- **Worldwide Commercial Use:**
  - >15,000 patients
Prohibitive Surgical Risk
DMR Cohort (n=127)

Age: 82 ±9 years
Prior MI: 24%
Prior stroke: 10%
Diabetes: 30%
COPD: 32%
Renal disease: 28%

Mean STS Risk
13.2%
Summary

- Mitral Clip therapy safely reduces DMR in patients at prohibitive risk for MV surgery
- In this group of prohibitive risk DMR patients, Mitral Clip therapy provides meaningful clinical improvements
  - Reduction of LV volumes
  - Improvements in NYHA Functional Class
  - Improvements in Quality of Life
  - Reduction in Hospitalizations for Heart Failure
ACC 2018

5-year clinical follow up
Prohibitive Risk-DMR Cohort

April | 2018
## Baseline Demographics and Co-morbidities

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>PR DMR (N=127)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, (mean ± SD)</td>
<td>82 ± 9 years</td>
</tr>
<tr>
<td>Core Lab Assessed MR ≥ 3+</td>
<td>90%</td>
</tr>
<tr>
<td>STS Mortality Risk, (mean ± SD)</td>
<td>13.2 ± 7.3%</td>
</tr>
<tr>
<td>NYHA Functional Class III or IV</td>
<td>87%</td>
</tr>
<tr>
<td>LV Ejection Fraction, (mean ± SD)</td>
<td>60.6 ± 9.5%</td>
</tr>
</tbody>
</table>
## Mitral Clip Therapy Continues to be Safe out to 5 years

### Key Measures of Device Safety

<table>
<thead>
<tr>
<th>Key Measures of Device Safety</th>
<th>Through 1 Year</th>
<th>1 Year to 5 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single Leaflet Device Attachment (SLDA)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>MV stenosis</td>
<td>3 (2.4%)</td>
<td>1 (0.8%)</td>
</tr>
<tr>
<td>Device Embolization</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

### Re-Interventions

<table>
<thead>
<tr>
<th>Re-Intervention</th>
<th># (%) of patients</th>
<th>Time to Re-Intervention Post-Index Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>MV Surgery Post-Index Procedure</td>
<td>4 (3.2%)</td>
<td>2, 26, 56, and 1,100 days</td>
</tr>
<tr>
<td>Second Intervention to Place an Additional MitraClip</td>
<td>3 (2.4%)</td>
<td>2.1, 4.2, and 4.9 years</td>
</tr>
</tbody>
</table>

Lim, Aliwadi, Kar et al. 2018 ACC Poster
Reduction in MR severity is durable out to 5 years

<table>
<thead>
<tr>
<th></th>
<th>MR ≤ 1+</th>
<th></th>
<th>MR ≤ 2+</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.0%</td>
<td>53.7%</td>
<td>0.0%</td>
<td>37.6%</td>
</tr>
<tr>
<td></td>
<td>0.0%</td>
<td>36.4%</td>
<td>0.0%</td>
<td>41.4%</td>
</tr>
<tr>
<td></td>
<td>8.9%</td>
<td>82.1%</td>
<td>9.4%</td>
<td>83.5%</td>
</tr>
<tr>
<td></td>
<td>6.8%</td>
<td>81.8%</td>
<td>6.9%</td>
<td>86.2%</td>
</tr>
</tbody>
</table>

Baseline Disch.  
Paired Analysis (N=123)

Baseline 1 Year  
Paired Analysis (N=85)

Baseline 3 Years  
Paired Analysis (N=44)

Baseline 5 Years  
Paired Analysis (N=29)
Improvement in Left Ventricular End Diastolic Volume is Durable out to 5 Years

Lim, Aliwadi, Kar et al. 2018 ACC Poster
Improvement in NYHA Functional Class is Durable out to 5 Years

<table>
<thead>
<tr>
<th>NYHA Class I</th>
<th>NYHA Class I and II:</th>
<th>Baseline 30 Days</th>
<th>Baseline 1 Year</th>
<th>Baseline 3 Years</th>
<th>Baseline 5 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.7%</td>
<td>33.6%</td>
<td>II</td>
<td>I</td>
<td>II</td>
<td>II</td>
</tr>
<tr>
<td>2.4%</td>
<td>40.5%</td>
<td>II</td>
<td>III</td>
<td>II</td>
<td>II</td>
</tr>
<tr>
<td>0.0%</td>
<td>34.8%</td>
<td>II</td>
<td>III</td>
<td>II</td>
<td>II</td>
</tr>
<tr>
<td>0.0%</td>
<td>39.3%</td>
<td>II</td>
<td>III</td>
<td>II</td>
<td>II</td>
</tr>
</tbody>
</table>

NYHA Class I: 2.7% 33.6% 2.4% 40.5% 0.0% 34.8% 0.0% 39.3%
NYHA Class I and II: 15.0% 82.3% 15.5% 86.9% 15.2% 78.3% 14.3% 82.1%

Lim, Aliwadi, Kar et al. 2018 ACC Poster
Successful Mitral Clip Procedure (Discharge MR≤2+) Resulted in Better Survival Through 5 Years

Overall Survival:
1 year = 75.4%
3 year = 51.0%
5 years = 34.6%

Note: p log-rank for discharge MR severity; unadjusted for differences in baseline characteristics.


Lim, Aliwadi, Kar et al. 2018 ACC Poster
MITRAL CLIP

WHAT ABOUT SECONDARY MITRAL REGURGITATION?
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.
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
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.

Randomize 1:1*

- MitraClip + GDMT
  N=305
- GDMT alone
  N=305

*Stratified by cardiomyopathy etiology (ischemic vs. non-ischemic) and site
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/m² in BMI >20 kg/m²
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 cm² by site-assessed TTE
7. Life expectancy <12 months due to non-cardiac conditions
# 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
# Powered Secondary Endpoints

- Tested in hierarchical order\(^1\) -

1. MR grade $\leq 2+$ 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
Primary Effectiveness Endpoint
All Hospitalizations for HF within 24 months

HR (95% CI) = 0.53 [0.40-0.70]  P<0.001

Cumulative HF Hospitalizations (n)

Time After Randomization (Months)

No. at Risk:

MitraClip + GDMT 283 in 151 pts
GDMT alone 160 in 92 pts

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

MitraClip 302 286 269 253 236 191 178 161 121
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]

GDMT alone

- 283/416.8 pt-yrs
- 67.9%

MitraClip + GDMT

- 160/446.5 pt-yrs
- 35.8%

HR (95% UCL] = 0.53 [0.66]
P<0.001

*Joint frailty model
Primary Safety Endpoint
Freedom from Device-related Complications within 12 months

MitraClip procedure attempted: N=293

- Device-related complications
  - 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%
**Powered Secondary Endpoints**

- Tested in hierarchical order\(^1\) -

<table>
<thead>
<tr>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. MR grade ≤2+ at 12 months</td>
</tr>
<tr>
<td>2. All-cause mortality at 12 months(^2)</td>
</tr>
<tr>
<td>3. Death and all HF hospitalization through 24 months (Finkelstein-Schoenfeld)</td>
</tr>
<tr>
<td>4. Change in QOL (KCCQ) from baseline to 12 months</td>
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<tr>
<td>5. Change in 6MWD from baseline to 12 months</td>
</tr>
<tr>
<td>6. All-cause hospitalizations through 24 months</td>
</tr>
<tr>
<td>7. NYHA class I or II at 12 months</td>
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<tr>
<td>8. Change in LVEDV from baseline to 12 months</td>
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<tr>
<td>9. All-cause mortality at 24 months</td>
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<tr>
<td>10. Death, stroke, MI, or non-elective CV surgery for device-related compls at 30 days(^3)</td>
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## Powered Secondary Endpoints

- Tested in hierarchical order\(^1\) -

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<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>MR grade (\leq 2+) at 12 months</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>2.</td>
<td>All-cause mortality at 12 months(^2)</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>3.</td>
<td>Death and all HF hospitalization through 24 months (Finkelstein-Schoenfeld)</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>4.</td>
<td>Change in QOL (KCCQ) from baseline to 12 months</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>5.</td>
<td>Change in 6MWD from baseline to 12 months</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>6.</td>
<td>All-cause hospitalizations through 24 months</td>
<td>0.03</td>
</tr>
<tr>
<td>7.</td>
<td>NYHA class I or II at 12 months</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>8.</td>
<td>Change in LVEDV from baseline to 12 months</td>
<td>0.003</td>
</tr>
<tr>
<td>9.</td>
<td>All-cause mortality at 24 months</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>10.</td>
<td>Death, stroke, MI, or non-elective CV surgery for device-related compls at 30 days(^3)</td>
<td>(&lt;0.001)</td>
</tr>
</tbody>
</table>

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**All-cause Mortality**

- **MitraClip + GDMT**
  - Time After Randomization (Months): 0, 3, 6, 9, 12, 15, 18, 21, 24
  - No. at Risk: 302, 286, 269, 253, 236, 191, 178, 161, 124
  - NNT (24 mo) = 5.9 [95% CI 3.9, 11.7]
- **GDMT alone**
  - Time After Randomization (Months): 0, 3, 6, 9, 12, 15, 18, 21, 24
  - No. at Risk: 312, 294, 271, 245, 219, 176, 145, 121, 88
  - HR [95% CI] = 0.62 [0.46-0.82]
  - P < 0.001

HR [95% CI] = 0.62 [0.46-0.82]
P < 0.001
MitraClip + GDMT
GDMT alone

All-cause Mortality or HF Hospitalization (%)

Time After Randomization (Months)

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

HR [95% CI] = 0.57 [0.45-0.71]
P<0.001

NNT (24 mo) = 4.5 [95% CI 3.3, 7.2]
Conclusions

• In pts with HF and moderate-to-severe or severe secondary MR who remained 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
CONCLUSIONS

I. Untreated severe MR is associated with an increase in morbidity and mortality.

II. The best treatment for primary MR is surgical repair. If a patient is not a surgical candidate, mitral clip therapy is beneficial.

III. For patients with secondary MR who fail GDMT, mitral clip therapy is beneficial and should be considered.
THANK YOU