Mitral Regurgitation: Causes, Natural History, Classic and Novel Interventions

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Conflicts

Consultant: Abbott, Edwards, Relypsy, Boehringer-Ingelheim, RESMED, Vwave, Cardiokinetics, Novartis

Grants: Astra-Zeneca, NIH, AHA
Mitral Regurgitation

- Epidemiology of Mitral Regurgitation (MR)
- *Primary vs Secondary (Functional)* MR
- *MR and prognosis*
- ACC/AHA Clinical Guidelines
- MITRA-FR and COAPT
- Benefits of medical and device therapy for secondary MR
- Role of the HF cardiologist pre and post MitraClip
- Some final thoughts
The most common valvular disorder in US\textsuperscript{1}

1 of 10 people over the age of 75 have moderate to severe MR\textsuperscript{1}

Of those referred 49% most are denied surgery due to age, comorbidities and LV dysfunction\textsuperscript{2}

\textsuperscript{1}Nkomo VT et al. Lancet 2006; 368:1004-11
\textsuperscript{2}Mirabel M et al. Eur Heart J 2007;28:1358-65
Classification of MR: Primary (degenerative) and Secondary (Functional)

**Primary (degenerative) MR**
- It’s the Valve!
- Anatomic abnormality of the mitral valve
  - Leaflets
  - Subvalvular apparatus
  - Chordae and papillary muscles

**Secondary (functional) MR**
- It’s the ventricle!
- LV dilation; often secondary to ischemic heart disease
  - Leads to mitral annular dilation
  - Incomplete coaptation of the mitral valve
Causes of MR: 
Primary (degenerative) and Secondary (Functional)

Primary degenerative) MR
- Mitral valve prolapse
- Rheumatic valve disease
- Trauma
- Flail leaflet (infection, rupture etc)
- Drugs
- Congenital

Secondary (functional) MR
- Myocardial infarction
- Dilated Cardiomyopathy
- Atrial fibrillation
Prevalence of Mitral Regurgitation in Chronic Systolic Heart Failure (LVEF ≤ 35% and NYHA III-IV)  n = 558

<table>
<thead>
<tr>
<th>Mitral Regurgitation</th>
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<tbody>
<tr>
<td>Absent or trace</td>
<td>10.8%</td>
</tr>
<tr>
<td>Mild</td>
<td>39.1%</td>
</tr>
<tr>
<td>Mild-moderate</td>
<td>11.1%</td>
</tr>
<tr>
<td>Moderate</td>
<td>21.9%</td>
</tr>
<tr>
<td>Moderate-severe</td>
<td>12.5%</td>
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<tr>
<td>Severe</td>
<td>4.3%</td>
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</tbody>
</table>

38.7 % with moderate or greater SMR and 17% with moderate-severe or >
Classification of MR: 
Primary (degenerative) and Secondary (Functional) 

Primary (degenerative) MR
It’s the Valve!

Secondary (functional) MR
It’s the ventricle!

Prognosis worsens as severity of MR worsens and repair or replacement improves prognosis

Prognosis worsens as severity of MR worsens but it is uncertain if repair or replacement improves prognosis
Survival worsens as FMR Increases in severity but we don’t know if fixing it improves mortality

Mitral Regurgitation

- Epidemiology of Mitral Regurgitation (MR)
- Primary vs Secondary (Functional) MR
- MR and prognosis
- ACC/AHA Clinical Guidelines
- MITRA-FR and COAPT
- Benefits of medical and device therapy for secondary MR
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2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

Developed in Collaboration With the American Association for Thoracic Surgery, American Society of Echocardiography, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons

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7.3.2. Medical Therapy

**CLASS I**

1. Patients with chronic secondary MR (stages B to D) and HF with reduced LVEF should receive standard GDMT therapy for HF, including ACE inhibitors, ARBs, beta blockers, and/or aldosterone antagonists as indicated (128,217-221). (Level of Evidence: A)

2. Cardiac resynchronization therapy with biventricular pacing is recommended for symptomatic patients with chronic severe secondary MR (stages B to D) who meet the indications for device therapy (222,223). (Level of Evidence: A)

7.3.3. Intervention

See Table 16 for a summary of recommendations for this section and Figure 4 for indications for surgery for MR.

**CLASS IIa**

1. Mitral valve surgery is reasonable for patients with chronic severe secondary MR (stages C and D) who are undergoing CABG or AVR. (Level of Evidence: C)

**CLASS IIb**

1. Mitral valve repair or replacement may be considered for severely symptomatic patients (NYHA class III to IV) with chronic severe secondary MR (stage D) who have persistent symptoms despite optimal GDMT for HF (224–235). (Level of Evidence: B)

2. Mitral valve repair may be considered for patients with chronic moderate secondary MR (stage B) who are undergoing other cardiac surgery. (Level of Evidence: C)
Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation


BACKGROUND
In patients who have chronic heart failure with reduced left ventricular ejection fraction, severe secondary mitral-valve regurgitation is associated with a poor prognosis. Whether percutaneous mitral-valve repair improves clinical outcomes in this patient population is unknown.

METHODS
We randomly assigned patients who had severe secondary mitral regurgitation (defined as an effective regurgitant orifice area of >20 mm² or a regurgitant volume of >30 ml per beat), a left ventricular ejection fraction between 15 and 40%, and symptomatic heart failure, in a 1:1 ratio, to undergo percutaneous mitral-valve repair in addition to receiving medical therapy (intervention group; 152 patients) or to receive medical therapy alone (control group; 151 patients).
MITRA-FR: No mortality benefit

Obadia J-F et al. NEJM 2018; August 27
TRANSCATHETER MITRAL-VALVE REPAIR IN PATIENTS WITH HEART FAILURE


ABSTRACT

BACKGROUND
Among patients with heart failure who have mitral regurgitation due to left ventricular dysfunction, the prognosis is poor. Transcatheter mitral-valve repair may improve their clinical outcomes.

METHODS
At 78 sites in the United States and Canada, we enrolled patients with heart failure and moderate-to-severe or severe secondary mitral regurgitation who remained symptomatic despite the use of maximal doses of guideline-directed medical therapy. Patients were randomly assigned to transcatheter mitral-valve repair plus medical therapy (device group) or medical therapy alone (control group). The primary effectiveness end point was all hospitalizations for heart failure within 24 months of follow-up. The primary safety end point was freedom from device-related complications.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Stone at Columbia University Medical Center, Cardiovascular Research Foundation, 1700 Broadway, 8th Fl., New York, NY 10019, or at gs2184@columbia.edu.

*A list of investigators, institutions, and research organizations participating in the COAPT trial is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on September 23, 2018, at NEJM.org.
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
COAPT: Key Inclusion Criteria

1. Ischemic or non-ischemic cardiomyopathy with LVEF 20%-50%
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. LVESD ≤70 mm
7. IC believes SMR can be successfully treated by the MitraClip
8. Guideline Directed Medical Therapy for HFrEF

Adjusted by a 4% reduction in the BNP or NT-proBNP cutoff for every increase of 1 kg/m² in BMI >20 kg/m²
COAPT: 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
## COAPT: Baseline Characteristics (i)

<table>
<thead>
<tr>
<th></th>
<th>MitraClip + GDMT (N=302)</th>
<th>GDMT alone (N=312)</th>
<th>MitraClip + GDMT (N=302)</th>
<th>GDMT alone (N=312)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>71.7 ± 11.8</td>
<td>72.8 ± 10.5</td>
<td>27.0 ± 5.8</td>
<td>27.1 ± 5.9</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>66.6%</td>
<td>61.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>35.1%</td>
<td>39.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>80.5%</td>
<td>80.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hyperchol.</strong></td>
<td>55.0%</td>
<td>52.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prior MI</strong></td>
<td>51.7%</td>
<td>51.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prior PCI</strong></td>
<td>43.0%</td>
<td>49.0%</td>
<td>7.8 ± 5.5</td>
<td>8.5 ± 6.2</td>
</tr>
<tr>
<td><strong>Prior CABG</strong></td>
<td>40.1%</td>
<td>40.4%</td>
<td>41.7%</td>
<td>43.6%</td>
</tr>
<tr>
<td><strong>Prior stroke or TIA</strong></td>
<td>18.5%</td>
<td>15.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PVD</strong></td>
<td>17.2%</td>
<td>18.3%</td>
<td>68.6%</td>
<td>69.9%</td>
</tr>
<tr>
<td><strong>COPD</strong></td>
<td>23.5%</td>
<td>23.1%</td>
<td>31.4%</td>
<td>30.1%</td>
</tr>
<tr>
<td><strong>H/o atrial fibr</strong></td>
<td>57.3%</td>
<td>53.2%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* STS repl score ≥8% or one or more factors present predicting extremely high surgical risk
<table>
<thead>
<tr>
<th>HF parameters</th>
<th>MitraClip + GDMT (N=302)</th>
<th>GDMT alone (N=312)</th>
<th>Echo core lab</th>
<th>MitraClip + GDMT (N=302)</th>
<th>GDMT alone (N=312)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology of HF</td>
<td></td>
<td></td>
<td>MR severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Ischemic</td>
<td>60.9%</td>
<td>60.6%</td>
<td>- Mod-to-sev (3+)</td>
<td>49.0%</td>
<td>55.3%</td>
</tr>
<tr>
<td>- Non-ischemic</td>
<td>39.1%</td>
<td>39.4%</td>
<td>- Severe (4+)</td>
<td>51.0%</td>
<td>44.7%</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
<td>EROA, cm²</td>
<td>0.41 ± 0.15</td>
<td>0.40 ± 0.15</td>
</tr>
<tr>
<td>- I</td>
<td>0.3%</td>
<td>0%</td>
<td>LVESD, cm</td>
<td>5.3 ± 0.9</td>
<td>5.3 ± 0.9</td>
</tr>
<tr>
<td>- II</td>
<td>42.7%</td>
<td>35.4%</td>
<td>LVEDD, cm</td>
<td>6.2 ± 0.7</td>
<td>6.2 ± 0.8</td>
</tr>
<tr>
<td>- III</td>
<td>51.0%</td>
<td>54.0%</td>
<td>LVESV, mL</td>
<td>135.5 ± 56.1</td>
<td>134.3 ± 60.3</td>
</tr>
<tr>
<td>- IV</td>
<td>6.0%</td>
<td>10.6%</td>
<td>LVEDV, mL</td>
<td>194.4 ± 69.2</td>
<td>191.0 ± 72.9</td>
</tr>
<tr>
<td>HF hosp w/i 1 year</td>
<td>58.3%</td>
<td>56.1%</td>
<td>LVEF, %</td>
<td>31.3 ± 9.1</td>
<td>31.3 ± 9.6</td>
</tr>
<tr>
<td>Prior CRT</td>
<td>38.1%</td>
<td>34.9%</td>
<td>- ≤40%</td>
<td>82.2%</td>
<td>82.0%</td>
</tr>
<tr>
<td>Prior defibrillator</td>
<td>30.1%</td>
<td>32.4%</td>
<td>RVSP, mmHg</td>
<td>44.0 ± 13.4</td>
<td>44.6 ± 14.0</td>
</tr>
</tbody>
</table>
## COAPT: Medication Use at Baseline

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

<table>
<thead>
<tr>
<th>Time After Randomization (Months)</th>
<th>MitraClip + GDMT</th>
<th>GDMT alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
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<tr>
<td>6</td>
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<tr>
<td>9</td>
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<td>21</td>
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<tr>
<td>24</td>
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No. at Risk:
- MitraClip: 302, 286, 269, 253, 236, 191, 178, 161, 124
- GDMT: 312, 294, 271, 245, 219, 176, 145, 121, 88

Median [25%, 75%] FU = 19.1 [11.9, 24.0] mos
COAPT: All-cause Mortality

HR [95% CI] = 0.62 [0.46-0.82]  
P<0.001

NNT (24 mo) = 5.9 [95% CI 3.9, 11.7]

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

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

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

\(^1\)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
FDA Approves MitraClip for Use in Heart Failure Patients With Functional Mitral Regurgitation

Transcatheter device now indicated for patients with degenerative or functional MR
Why are the COAPT Results so Different from MITRA-FR? Possible Reasons

<table>
<thead>
<tr>
<th></th>
<th>MITRA-FR (n=304)</th>
<th>COAPT (n=614)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severe MR entry criteria</strong></td>
<td>Severe FMR by EU guidelines: EROA &gt;20 mm$^2$ or RV &gt;30 mL/beat</td>
<td>Severe FMR by US guidelines: EROA &gt;30 mm$^2$ or RV &gt;45 mL/beat</td>
</tr>
<tr>
<td><strong>EROA (mean ± SD)</strong></td>
<td>31 ± 10 mm$^2$</td>
<td>41 ± 15 mm$^2$</td>
</tr>
<tr>
<td><strong>LVEDV (mean ± SD)</strong></td>
<td>135 ± 35 mL/m$^2$</td>
<td>101 ± 34 mL/m$^2$</td>
</tr>
<tr>
<td><strong>GDMT at baseline and FU</strong></td>
<td>Receiving HF meds at baseline – allowed variable adjustment in each group during follow-up per “real-world” practice</td>
<td>CEC confirmed pts were failing maximally-tolerated GDMT at baseline – few major changes during follow-up</td>
</tr>
<tr>
<td><strong>Acute results: No clip / ≥3+ MR</strong></td>
<td>9% / 9%</td>
<td>5% / 5%</td>
</tr>
<tr>
<td><strong>Procedural complications</strong>*</td>
<td>14.6%</td>
<td>8.5%</td>
</tr>
<tr>
<td><strong>12-mo MitraClip ≥3+ MR</strong></td>
<td>17%</td>
<td>5%</td>
</tr>
</tbody>
</table>

*MITRA-FR defn: device implant failure, transf or vasc compl req surg, ASD, card shock, cardiac embolism/stroke, tamponade, urg card surg
**Time to First HFH or All-Cause Mortality**

Randomization Groups Stratified by 30-day Residual MR

**MitraClip + GDMT**

- MR 0/1+ (N=202; 72.9%)  
- MR 2+ (N=55; 19.9%)  
- MR 3+/4+ (N=20; 7.2%)

**GDMT Only**

- MR 0/1+ (N=21; 8.2%)  
- MR 2+ (N=67; 26.1%)  
- MR 3+/4+ (N=169; 65.8%)

### # At Risk

<table>
<thead>
<tr>
<th>MR 0/1+</th>
<th>202</th>
<th>176</th>
<th>139</th>
<th>106</th>
<th>66</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR 2+</td>
<td>55</td>
<td>45</td>
<td>37</td>
<td>31</td>
<td>21</td>
</tr>
<tr>
<td>MR 3+/4+</td>
<td>20</td>
<td>13</td>
<td>7</td>
<td>7</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MR 0/1+</th>
<th>21</th>
<th>16</th>
<th>13</th>
<th>11</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR 2+</td>
<td>67</td>
<td>56</td>
<td>44</td>
<td>26</td>
<td>15</td>
</tr>
<tr>
<td>MR 3+/4+</td>
<td>169</td>
<td>107</td>
<td>76</td>
<td>44</td>
<td>26</td>
</tr>
</tbody>
</table>

**P = 0.001 Overall**

HR [95% CI] = 0.75 [0.48, 1.18] for 0/1+ vs 2+

HR [95% CI] = 0.36 [0.20, 0.64] for 0/1+ vs 3+/4+

HR [95% CI] = 0.48 [0.25, 0.92] for 2+ vs 3+/4+

**P = 0.930**

**P < 0.001 Overall**

HR [95% CI] = 0.84 [0.38, 1.84] for 0/1+ vs 2+

HR [95% CI] = 0.44 [0.21, 0.90] for 0/1+ vs 3+/4+

HR [95% CI] = 0.50 [0.34, 0.76] for 2+ vs 3+/4+
Proportionate vs Dis-Proportionate MR???
MITRA-FR “Like” Patients from COAPT

Lindenfeld J et al. Presented at AATS May 2019
KCCQ Improvement in Group 1 and 2

Group 1: KCCQ Improvement*

- MitraClip+ GDMT
- GDMT Alone

P = 0.011

*Analyzed using Analysis of Covariance (ANCOVA)

Group 2: KCCQ Improvement*

- MitraClip+ GDMT
- GDMT Alone

P < 0.001

*Analyzed using Analysis of Covariance (ANCOVA)
6MWD Improvement In Substudy Analysis

**Group 1: 6MWD Improvement***

- **MitraClip + GDMT**
- **GDMT Alone**

P = 0.016

**Group 2: 6MWD Improvement***

- **MitraClip + GDMT**
- **GDMT Alone**

P = 0.112

*Analyzed using ANCOVA model*
Mitral Regurgitation

- Epidemiology of Mitral Regurgitation (MR)
- *Primary vs Secondary (Functional) MR*
- **MR and prognosis**
- ACC/AHA Clinical Guidelines
- MITRA-FR and COAPT
- Benefits of medical and device therapy for secondary MR
- Role of the HF cardiologist pre and post MitraClip
- Some final thoughts
Higher Doses of RAAS inhibitors and Beta Blockers Are Associated with Improved Mortality Following CRT
Role of the Heart Failure Specialist in the Post-COAPT World

- Refer the patients already in Heart Failure clinics
- Get to maximally tolerated GDMT
  - Screening for Guideline Directed Medical Therapy (GDMT)
  - Document reasons for lack of GDMT
- Why is GDMT so important?
  - Mortality benefits
  - Reduction in mitral regurgitation (MR)
- Referred patients not in a HF clinic are rarely on maximally tolerated GDMT
- Uptitrating GDMT after MitraClip®
Are we asking the right questions?

Tug was asked when pitching in Houston if he preferred grass or Astroturf

"I dunno. I never smoked any Astroturf."