Transcatheter Mitral Repair and Replacement: Data, Devices, and Patient Selection

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TYPES OF MITRAL REGURGITATION

MITRAL REGURGITATION

PRIMARY (DEGENERATIVE)

SECONDARY (FUNCTIONAL)
TYPES OF MITRAL REGURGITATION

PRIMARY (DEGENERATIVE)

SECONDARY (FUNCTIONAL)
# CHRONIC PRIMARY MITRAL REGURGITATION: 2017 ACC/AHA GUIDELINES FOR INTERVENTION

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
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<tbody>
<tr>
<td>MV surgery is recommended for symptomatic patients with chronic severe primary MR (stage D) and LVEF &gt;30%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MV surgery is recommended for asymptomatic patients with chronic severe primary MR and LV dysfunction (LVEF 30%–60%) and/or LVESD ≥40 mm, stage C2</td>
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<tr>
<td>New: Mitral valve surgery is reasonable for asymptomatic patients with chronic severe primary MR (stage C1) and preserved LV function (LVEF &gt;60% and LVESD &lt;40 mm) with a progressive increase in LV size or decrease in EF on serial imaging studies</td>
<td>C-LD</td>
<td></td>
</tr>
</tbody>
</table>

Consider surgery *when*:
- Symptoms
- **or**
  - LV dysfunction (EF<60%, ESD≥40mm) or worsening dysfunction/volume

Don’t sit and wait!!!
“Watchful waiting” is associated with greater long-term survival and a lower risk of heart failure.

SURVIVAL STRATIFIED BY LA ENLARGEMENT IN DMR PATIENTS

A

OVERALL SURVIVAL

B

SURVIVAL UNDER MEDICAL MANAGEMENT

C

POST-OPERATIVE SURVIVAL

Survival (%)

Follow-Up (Years)

Follow-Up (Years)

Follow-Up (Years)

Patients at risk

<40 ml/m²  40-59 ml/m²  ≥60 ml/m²

Essayagh B ... Enrique-Sarano M al, JACC 2019;74:858-70
Secondary MR is a Predictor of Mortality

- Increasing Mitral Regurgitation
- Dilation of Left Ventricle
- Dysfunction of Left Ventricle
- Increase Load/Stress
- Muscle Damage/Loss

1 year mortality up to 57%

No/mild SMR

Moderate SMR

Severe SMR

Graph courtesy of Dr. G Stone.
### Current Heart Failure Guidelines: GDMT and CRT

**NO TREATMENT OPTIONS FOR PATIENTS WHO REMAIN SYMPTOMATIC DESPITE BEING ON MAXIMALLY TOLERATED GDMT**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Class</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I A</td>
<td></td>
<td>Patients with chronic secondary MR (stages B to D) and HF with reduced LVEF should receive <strong>standard GDMT therapy for HF</strong>, including ACE inhibitors, ARBs, beta blockers, and/or aldosterone antagonists as indicated</td>
</tr>
<tr>
<td>I A</td>
<td></td>
<td><strong>Cardiac resynchronization therapy</strong> with biventricular pacing is recommended for symptomatic patients with chronic severe secondary MR (stages B to D) who meet the indications for device therapy</td>
</tr>
<tr>
<td>IIa C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIb B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIb C</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
TRANSCATHETER APPROACHES TO MITRAL REGURGITATION

Leaflet Repair
- MitraClip
- Pascal

Annuloplasty
- Direct
- Indirect
  - Cardioband
  - Millipede
  - Amend
  - Carillon
  - MVRx
  - Cerclage

Valve Replacement
- Transseptal
- Trans-apical
  - Intrepid
  - Tendyne
U.S. MITRACLIP INDICATION FOR USE: "PROHIBITIVE RISK" PRIMARY MR (DEGENERATIVE MR)

- Significant symptomatic degenerative (primary) MR (≥ 3+)
- Determined to be at prohibitive risk for mitral valve surgery by a heart team, which includes a cardiac surgeon experienced in mitral valve surgery
WHAT IS PROHIBITIVE SURGICAL RISK?

- 30-day STS predicted operative mortality risk score of $\geq 8\%$ for patients deemed likely to undergo mitral valve replacement or $\geq 6\%$ for patients deemed likely to undergo mitral valve repair.
- Porcelain aorta or extensively calcified ascending aorta.
- Frailty (assessed by in-person cardiac surgeon consultation).
- Hostile chest.
- Severe liver disease / cirrhosis (MELD Score $>12$).
- Severe pulmonary HTN (systolic PAP $>2/3$ systemic pressure).
- Unusual extenuating circumstance, such as RV dysfunction with severe TR, chemotherapy for malignancy, major bleeding diathesis, immobility, AIDS, severe dementia, high risk of aspiration, internal mammary artery (IMA) at high risk of injury, etc.
83 YR OLD MALE, SEVERE SYMPTOMATIC MR DUE TO FLAIL P2 SCALLOP
ONE CLIP, TRACE MR, GRADIENT = 3MMHG, D/C’D POST-PROCEDURE DAY #1, COMPLETE RESOLUTION OF SYMPTOMS
# Transcatheter Mitral Valve Repair with the MitraClip: The Scripps Experience

## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>N=261</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, yrs (median, range)</strong></td>
<td>83 (28-99)</td>
</tr>
<tr>
<td><strong>Male sex</strong></td>
<td>145 (55.6%)</td>
</tr>
<tr>
<td><strong>STS predicted mortality, repair</strong> (mean ± SD)</td>
<td>8.2 ± 8.5</td>
</tr>
<tr>
<td><strong>STS predicted mortality, replacement</strong> (mean ± SD)</td>
<td>10.6 ± 8.8</td>
</tr>
<tr>
<td><strong>KCCQ Overall Summary Score</strong></td>
<td>49.0 ± 23.0</td>
</tr>
<tr>
<td><strong>NYHA Class III/IV</strong></td>
<td>221 (84.7%)</td>
</tr>
<tr>
<td><strong>Mechanism of MR</strong></td>
<td></td>
</tr>
<tr>
<td>Degenerative</td>
<td>177 (67.8%)</td>
</tr>
<tr>
<td>Functional</td>
<td>35 (13.4%)</td>
</tr>
<tr>
<td>Mixed</td>
<td>48 (18.4%)</td>
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</tbody>
</table>
TRANSCATHETER MITRAL VALVE REPAIR WITH THE MITRACLIP: THE SCRIPPS EXPERIENCE

PROCEDURAL CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>N=261</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of clips</strong> implanted per procedure (mean)</td>
<td>1.8</td>
</tr>
<tr>
<td><strong>Concomitant tricuspid repair</strong></td>
<td>20</td>
</tr>
<tr>
<td><strong>In-Hospital Adverse Events</strong></td>
<td></td>
</tr>
<tr>
<td>Urgent cardiac surgery</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>0</td>
</tr>
<tr>
<td>Stroke</td>
<td>2 (0.76%)</td>
</tr>
<tr>
<td>Pericardial effusion requiring drainage</td>
<td>2 (0.76%)</td>
</tr>
<tr>
<td>Death (procedure-related)*</td>
<td>2 (0.76%)</td>
</tr>
<tr>
<td><strong>Length-of-stay</strong> post-procedure, days (median, IQR)</td>
<td>1 (1,3)</td>
</tr>
<tr>
<td><strong>Discharge to Home</strong></td>
<td>221 (84.7%)</td>
</tr>
</tbody>
</table>

*5 non-procedure related deaths: 3 with successful TMVRep for pap muscle rupture or cardiogenic shock; 1 without device implant
TMV REPAIR WITH THE MITRA CLIP: THE SCRIPPS EXPERIENCE

Magnitude of MR At Baseline And Over Follow-Up

<table>
<thead>
<tr>
<th>MR Severity</th>
<th>Baseline</th>
<th>Discharge</th>
<th>1 month</th>
<th>1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>4+</td>
<td>77.0%</td>
<td>83.5%</td>
<td>72.7%</td>
<td>70.0%</td>
</tr>
<tr>
<td>2+</td>
<td></td>
<td></td>
<td></td>
<td>16.3%</td>
</tr>
<tr>
<td>3+</td>
<td>22.2%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Baseline, Discharge, 1 month, 1 year
MITRACLIP REDUCES LEFT VENTRICULAR VOLUMES: THE SCRIPPS EXPERIENCE

**Baseline** vs. **One Month**
- LVEDVi: 68.4 vs. 63.1
- **p<0.0001**
- N=166

**Baseline** vs. **One Year**
- LVEDVi: 65.0 vs. 58.1
- **P=0.009**
- N=64
QUALITY OF LIFE AFTER TRANSCATHETER MITRAL VALVE REPAIR: THE SCRIPPS EXPERIENCE

KCCQ Over Time

Mean change in KCCQ

KCCQ Change From Baseline (Paired)

Baseline 1 month 1 year

- Baseline: 49.0 ±23.0
- 1 month: 71.8 ±22.5
- 1 year: 76.6 ±23.3

To 1 month

- SCRIPPS CLINIC

To 12 months

- P<0.001
- P=0.01

N=198
N=93

- 1 month: 21.9 ±24.8
- 12 months: 22.8 ±28.3
TRANSCATHETER MITRAL VALVE REPAIR: SITE VOLUMES ACROSS THE GREATER SAN DIEGO AREA

- SCRIPPS MEMORIAL HOSPITAL LA JOLLA-27616*
- SHARP MEMORIAL HOSPITAL-27008
- ST JOSEPH HOSPITAL-27638
- LOMA LINDA MERCANTILE-36526
- HOAG MEMORIAL HOSP PRESBYTERIAN-30673
- UNIVERSITY OF CA SAN DIEGO MED CTR-27179
- KAISER FOUNDATION HOSPITAL-38997
- ST BERNARDINE MEDICAL CENTER-28370
- EISENHOWER MEDICAL CENTER-28962
- KAISER FOUNDATION HOSPITAL-38997
Procedural Success: Learning Curve Analysis*

Acceptable (≤2+ residual MR)

92% 93% 95%

Optimal (≤1+ residual MR)

65% 73% 80%

*Curves generated using hierarchical generalized linear mixed models
Procedure Time and Procedural Complications*

**Procedure Time**

- **Case Time in Minutes**
  - Procedure sequence number (for Operators)
  - Unadjusted P: <0.001, Adjusted P: <0.001
  - Association: <0.001, Linearity: <0.001

**Procedural Complications**

- **Composite of Complications %**
  - Procedure sequence number (for Operators)
  - Unadjusted P: <0.001, Adjusted P: <0.001
  - Association: <0.001, Linearity: 0.162

*Curves generated using hierarchical generalized linear mixed models*
55 yr-old F with Non-Ischemic Dilated CM, EF 36%, Narrow QRS, NYHA Class III Symptoms Despite Optimal Medical Therapy (Entresto/Beta-Blocker/Aldactone)

- Echocardiography:
  - normal leaflets and apparatus
  - apical displacement (tenting) of mitral valve leaflets
  - LVESD 5.2 cm
  - EROA 0.41cm², RV 64ml/beat, RF 65%, consistent with severe functional mitral regurgitation (FMR) according to American Society of Echo criteria
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
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]

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events</th>
<th>Person-Years</th>
<th>Rate</th>
<th>HR (95% UCL)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDMT alone</td>
<td>283</td>
<td>416.8</td>
<td>67.9%</td>
<td>0.53 [0.66]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MitraClip + GDMT</td>
<td>160</td>
<td>446.5</td>
<td>35.8%</td>
<td>0.53 [0.66]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Joint frailty model
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]

<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>29.1%</td>
<td>46.1%</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
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<tr>
<td>9</td>
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<td>12</td>
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<td>15</td>
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<tr>
<td>18</td>
<td></td>
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<tr>
<td>21</td>
<td></td>
<td></td>
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<tr>
<td>24</td>
<td></td>
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</tbody>
</table>

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
Primary Safety Endpoint
Freedom from Device-related Complications within 12 months

MitraClip procedure attempted

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device-related complications</td>
<td>9 (3.4%)</td>
</tr>
<tr>
<td>- Single leaflet device attachment</td>
<td>2 (0.7%)</td>
</tr>
<tr>
<td>- Device embolization</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>- Endocarditis requiring surgery</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>- Mitral stenosis requiring surgery</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>- Left ventricular assist device implant</td>
<td>3 (1.2%)</td>
</tr>
<tr>
<td>- Heart transplant</td>
<td>2 (0.8%)</td>
</tr>
<tr>
<td>- Any device-related complication requiring non-elective CV surgery</td>
<td>1 (0.3%)</td>
</tr>
</tbody>
</table>

P<0.001

96.6%* 94.8% [95% LCL] 88% OPC

*KM estimate; **Calculated from Z test with Greenwood’s method of estimated variance against a pre-specified objective performance goal of 88%
A: Cause Mortality or HF Hospitalization

All patients, ITT, including crossovers

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

- MitraClip + GDMT
- GDMT alone

# at Risk:

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td>MitraClip + GDMT</td>
<td>302</td>
<td>238</td>
<td>196</td>
<td>176</td>
<td>148</td>
<td>101</td>
<td>66</td>
</tr>
<tr>
<td>GDMT alone</td>
<td>312</td>
<td>206</td>
<td>156</td>
<td>120</td>
<td>87</td>
<td>37</td>
<td>20</td>
</tr>
</tbody>
</table>

HR [95% CI] = 0.48 [0.39, 0.59]
P = 0.0000000000001
NNT = 3.4 [95% CI 2.7, 4.6]
NNT = 4.5 [95% CI 3.3, 7.0]
New U.S. MitraClip Indication For Use: Secondary (Functional) MR

- Symptomatic moderate-to-severe or severe secondary (functional) MR (≥ 3+ per ASE criteria) despite maximally tolerated GDMT
- LV ejection fraction ≥ 20%
- LV end-systolic dimension (LVESD) ≤ 70mm
- As determined by a multidisciplinary heart team experienced in the treatment of heart failure and mitral valve disease
UNMET CLINICAL NEED DESPITE SUCCESS OF TMV REPAIR WITH MITRACLIP

- Patients who are poor/not anatomic candidates
  - Small MVOA
  - Calcified, thickened leaflets
  - Cleft leaflets
  - Barlow’s type valve/multi-segment flail
  - Some post-surgical repair

- Consistent MR reduction to 1+ or less?
Transcatheter MV Repair: **Device Landscape 2019**

**Edge-to-edge**
- Abbott MitraClip***
- Edwards Pascal*
- MitraFlex

**Direct and indirect annuloplasty**
- CDI Carillon**
- Mitralign TAMR**
- Edwards Cardioband**
- Ancora Heart Accucinch*
- Millipede IRIS*
- MVRx Arto*
- Mardil VenTouch*
- Mitraspan TASRA*
- Valcare Amend*
- Micardia enCor*
- MitraLoop Cerclage*
- Cardiac Implants RDS*
- QuantumCor (RF)
- Valfix

**MV replacement**
- Edwards CardiAQ*
- Edwards Sapien M3*
- Neovasc Tiara*
- Abbott Tendyne*
- Medtronic Intrepid*
- HighLife*
- Caisson*
- NCSI NaviGate*
- MValve*
- CardioValve*
- Cephea*
- St. Jude
- Micro Interventional
  - ValveXchange
  - MitrAssist
  - Braile Quattuor
  - Direct Flow
  - Sinomed Accufit
  - Valcare Corona
  - Epigen

**MV replacement (cont)**
- MitralHeal
- HT Consultant Saturn
- Lutter valve
- Transcatheter Technologies
  - Tresillo
  - Venus
  - Verso
- Transmural Systems
- Saturn (InnovaHeart)
- 4C Altara

**Other approaches**
- NeoChord DS 1000**
- Harpoon neochords*
- Babic chords*
- Pipeline Medical (Gore)
- Middle Peak Medical*
- St. Jude leaflet plication*
- Cardiosolutions Mitra-Spacer*
  - Mitralix*
- Mitraltech Vchordal
- Coramaze Mitramaze

*In patients
*CE mark
*FDA approved

Stone, G. TVT 2019
Edwards PASCAL Transcatheter Valve Repair System

Implant

Central spacer intended to fill the regurgitant orifice area

Spacer and broad, contoured paddle design reduce stress on leaflets

Clasps allow for independent leaflet capture and the ability to fine-tune leaflet position

CAUTION: Investigational device. Limited by Federal (or United States) law to investigational use.
The Standard of Surgical MR Repair: Mitral Ring Annuloplasty

Primary MR Repair: Adjunctive

- Reduces annular circumference
- Reduces septal-lateral diameter

Secondary MR Annuloplasty: Stand Alone

Modified from Rogers, J. Presented at CRT 2019
Millipede Transcatheter Annuloplasty Ring System

Design Goals
- Physiologically sound mechanism of action replicates the cornerstone of surgical repair
- Customizable, repositionable and retrievable
- Leaves options open for future interventions
- Familiar controls and ICE-guided placement for streamlined procedure
- Transfemoral-transseptal access

Placement  Anchor  Actuate

Technology under development. Not available for sale.
Millipede Transcatheter Annuloplasty Ring System with Integrated ICE Imaging
Medtronic Intrepid TMVR
**TRIAL DESIGN**

Principal Investigators: Dr. David Adams and Dr. Marty Leon
Study Chair: Dr. Michael Mack

Evaluate the safety and efficacy of the Medtronic Intrepid™ TMVR System in patients with symptomatic mitral regurgitation.

**ASSESSMENT BY MULTIDISCIPLINARY HEART TEAM**

1:1 Randomization

- Treatment Arm TMVR
- Control Arm MV Surgery

Single-arm Cohort

- TMVR

Ineligible for surgical procedure
APOLLO TMVR - THE SCRIPPS EXPERIENCE

- 3 implants performed to date
- Enrollment challenges: anatomy excludes many patients
  - Risk of LVOT obstruction
  - Annular dimensions
  - Severe annular calcification
  - Severe RV dysfunction

Anatomy Exclusions

- LVOTO: 13%
- Small Annulus: 4%
- Large Annulus: 22%
- Prohibitive MAC: 9%
- Interaction with TAVR valve: 52%

N = 23 patients
INTREPID TMVR: CT AT 1 MONTH FOLLOW-UP IN FIRST PATIENT TREATED AT SCRIPPS
APOLLO TMVR TRIAL STATUS

- 750+ patients consented
- 190+ patients enrolled
- 55 US Sites participating
- For “roll-in” patients 30 day mortality after TMVR = 2% (n=51)
SAPIEN M3: Pursuing Safe & Effective Transfemoral Valve Replacement to Eliminate Mitral Regurgitation

U.S. Pivotal Trial

**Innovation**

- Low-profile, Transfemoral easy-to-use delivery system
- Modified SAPIEN 3 29mm valve leverages proven design
- Docking system facilitates valve anchoring;
- Retrievability allows for optimal device placement

**Evidence**

In 15 patient EFS early clinical experience:

- High technical success, 93% reduction of MR to 0 or 1+; no deaths from any cause at 30 days¹

Experience in 30+ patients

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2019

Continued Early Feasibility Studies

Plan to initiate U.S. Pivotal Trial in late 2019
TRILUMINATE Pivotal Study Design

**TRIAL DESIGN**

- Prospective, randomized, controlled, multi-center trial
- **450** subjects enrolled at up to 80 sites in the US, Canada, Europe
  - Primary endpoint to be assessed after 350 subjects reach 12 month follow-up
  - Adaptive design incorporated, in case study is under-powered to show a difference

**SCIENTIFIC OBJECTIVE**

- To evaluate the safety and effectiveness of the TriClip device in improving clinical outcomes in symptomatic patients with severe tricuspid regurgitation (TR) who have been determined by the site’s local heart team to be at intermediate or greater estimated risk for mortality with tricuspid valve surgery

**PRIMARY ENDPOINT**

**Randomized Arm**
A composite of mortality or tricuspid valve surgery, heart failure hospitalizations, and quality of life improvement assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ), evaluated at 12 months in a hierarchical fashion using the Finkelstein-Schoenfeld methodology

**Single Arm:**
Survival and quality of life improvement (assessed using KCCQ) at 12 months compared to baseline. In this cohort of sick patients in which it is believed TR cannot be reduced to moderate or less, it is expected that there will be significant improvement in quality of life at 12 months post enrollment

CAUTION: Investigational device. Limited by federal (U.S.) law to investigational use only. Not available for sale.
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THE MITRAL VALVE IS GETTING POPULAR!
Ninth Annual
Structural Heart Intervention and Imaging 2020: A Practical Approach
February 5-7, 2020 • Hyatt Regency at Aventine • La Jolla, California

Visit www.scripps.org/shicme for course updates!