### MHIF FEATURED STUDY: ATTR CM

**CONTRIBUTION:** Transthyretin-Mediated Amyloid Cardiomyopathy  
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**SPONSOR:** Ionis Pharmaceuticals

### DESCRIPTION: A Phase 3 Global, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ION-682884 in Patients with Transthyretin-Mediated Amyloid Cardiomyopathy

ION-682884 vs. placebo administered by subcutaneous injection once every 4 weeks in patients with ATTR-CM receiving available background therapy. ION-682884 is a ligand-conjugated antisense drug designed to reduce the production of transthyretin to treat all types of TTR amyloidosis.

### CRITERIA LIST/QUALIFICATIONS:

**Inclusion**
- Amyloid deposits in cardiac or non-cardiac tissue
- Medical history of HF secondary to hereditary or wild-type ATTR-CM

**Exclusion**
- Cardiomyopathy not primarily caused by ATTR-CM
- Significant co-morbidities
- Current treatment with inotersen, patisiran, diflunisal, doxycycline, non-dihydropyridine calcium-channel blocker
CASE PRESENTATION - 2015

• 77 year old lady – severe AS
• PMH
  • peripheral arterial disease with stents in the iliofemoral vessels,
  • COPD
  • Parkinson’s
  • CHB s/p PPM
  • HTN
  • HL
  • CAD s/p RCA-BMS in 8/2013
  • Atrial fibrillation
ECHO CARDIOGRAM 2015

- The aortic valve is tricuspid-calcified and sclerotic, moderate to severe stenosis and mild regurgitation.
- Peak velocity is 3.4 m/second, mean gradient is 28 mm Hg, valve area is 0.84 cm squared, and dimensionless index is 0.23

Dobutamine Stress Echo 2015

- The aortic valve is calcified, severe aortic stenosis. AVA is 0.7cm2 at rest. With dobutamine, Vmax increases to 4.2-4.3 m/sec.

2015 TAVR – TRANSAORTIC
POST PROCEDURE ECHO

• 23 mm SapienXT bioprosthesis in the aortic position with mean gradient of 11.6 mmHg, dimensionless index of 0.54, EOA of 1.5 cm², and mild anteromedial paravalvular regurgitation.

CASE PRESENTATION - 2020

• Developed symptoms of HF
CASE PRESENTATION - 2020

WHAT TO DO NOW?!
OBJECTIVE

• Background on longevity of these valves and mechanism of deterioration
• Management of TAVR failure – Surgery vs Redo TAVR
• Limitation of TAVR in TAVR
• Bench testing
• Coronary protection: Chimney stent and Basilica

MECHANISM OF TAVR FAILURE
Bioprosthetic Valve Dysfunction

- **Structural Valve Deterioration**
  - Intrinsic permanent changes of the prosthetic valve (i.e., calcification, leaflet fibrosis, tear or flail) leading to degeneration and/or haemodynamic dysfunction

- **Nonstructural Valve Deterioration**
  - Any abnormality not intrinsic to the prosthetic valve itself (i.e., para-prosthetic regurgitation, prosthesis malposition, patient-prosthesis mismatch, late embolization) leading to degeneration and/or dysfunction

- **Thrombosis**
  - Thrombus development on any structure of the prosthetic valve, leading to dysfunction with or without thromboembolism

- **Endocarditis**
  - Infection involving any structure of the prosthetic valve, leading to perivalvular abscess, dehiscence, pseudoaneurysms, fistulas, vegetations, cusp rupture or perforation

LONGEVITY OF TAVR VALVES
Bioprosthetic Valve Failure:
1) Valve dysfunction with clinically expressive criteria or irreversible stage 3 (severe) hemodynamic valve deterioration;
2) Valve reintervention
3) Valve-related death
VALVE DETERIORATION – TAVR VS SAVR

5-Year Exposure-Adjusted Incidence Rates (per 100 Patient-Years)

- SAPIEN XT TAVR: 1.61%
- SAPIEN 3 TAVR: 0.68%
- SAVR: 0.60%

p < 0.01 (except *p > 0.004 by IPTW)

Percentage of BVF Cases Related to SVD: 64.0% for SAPIEN XT TAVR, 37.5% for SAVR, 32.0% for SAPIEN 3 TAVR.

CAUSES OF VALVE FAILURE

- SAPIEN XT TAVR (n = 25):
  - SVD: 64%
  - Paravalvular AR: 20%
  - Valve Migration: 8%
  - Endocarditis: 8%

- SAPIEN 3 TAVR (n = 19):
  - SVD: 58%
  - Paravalvular AR: 32%
  - Endocarditis: 5%

- SAVR (n = 8):
  - SVD: 12.5%
  - Paravalvular AR: 37.5%
  - Valve Migration: 37.5%
  - Endocarditis: 12.5%

Pibarot, P et al, JACC 2020
TYPE OF VALVE REINTERVENTION

SAPIEN XT TAVR (n = 21)
- n = 17 (81%)
- n = 3 (14%)
- n = 1 (5%)

SAVR (n = 6)
- n = 5 (83%)
- n = 1 (17%)

SAPIEN 3 TAVR (n = 17)
- n = 13 (76%)
- n = 4 (24%)

Pibarot, P et al, JACC 2020

MANAGEMENT OF FAILING TAVRS
MANAGEMENT OF FAILING TAVRS

Surgery

Redo TAVR

TAVR EXPLANT CONSIDERATION

• Overall mortality of SAVR after TAVR remains ~10%
• Meticulous surgical technique is required in these commonly intermediate to high-risk surgical patients

• May need root replacement if the valve was implanted > 1 year (Thorani), particularly in Evulot
Indication for the explant:
- Endocarditis 20.7%
- Bioprosthetic failure 79.3%

Hirji et al., JACC 2020
TAVR EXPLANT REGISTRY

Hirji et al, JACC 2020

TAVR in TAVR
CONCERNS ABOUT REDO TAVR

• Unknown Safety / Mortality
• Challenging Coronary Access
• Coronary Obstruction
• Patient Prosthesis Mismatch
• Uncertainty Valve choice / sizing / positioning

OUTCOMES OF TAVR IN TAVR
REDO TAVR REGISTRY

- The Redo-TAVR registry collected data on consecutive patients who underwent redo-TAVR at 37 centers

- Patients were classified as:
  - Probable TAVR failure (procedure related; <1 year of index TAVR)
  - Probable THV failure (Prosthesis related; >1 year of index TAVR)

Landes U, JACC 2020
REDO TAVR REGISTRY

- Median follow-up (post redo-TAVR) was 15 (3 to 36) months

- Similar model was used in 60% of the patients
  - Corevalve (37%)
  - Sapien XT (24%)

Index TAVR

- Redo TAVR (N=212)
  - Balloon Expandable (N=82; 39%)
  - Self-Expandable (N=130; 61%)

Redo TAVR

- Balloon Expandable (N=51; 62%)
- Self-Expandable (N=31; 38%)
- Balloon Expandable (N=56; 43%)
- Self-Expandable (N=74; 57%)

Landes U, JACC 2020
### SIZING FOR REDO TAVR

<table>
<thead>
<tr>
<th>1st THV (mm)</th>
<th>20</th>
<th>23</th>
<th>25</th>
<th>26</th>
<th>27</th>
<th>29</th>
<th>31</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>23</td>
<td>0</td>
<td>36</td>
<td>0</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>24</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>25</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>26</td>
<td>0</td>
<td>5</td>
<td>1</td>
<td>46</td>
<td>2</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>27</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>29</td>
<td>0</td>
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<tr>
<td>34</td>
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<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

*Landes U, JACC 2020*

### REDO TAVR OUTCOMES

**Redo-TAVR: Overall Patients**

- All-Cause Mortality (%)
- Time Since Redo TAVR, Months
- Number at risk: 212, 200, 181, 164, 153, 150, 149, 143, 139, 133, 129, 127

- Median follow-up time was 447 (95 to 1,091) days

**Redo-TAVR: THV Failure Patients**

- All-Cause Mortality (%)
- Time Since Redo TAVR, Months
- Number at risk: 85, 81, 74, 65, 59, 58, 57, 54, 52, 50, 50

- Number at risk: AR or Mixed, AS
- Number at risk: 47, 38, 36, 34, 33, 31, 31, 31, 30, 30

*Landes U, JACC 2020*
- Transvalvular gradients decreased markedly with a mean of 12.6 +/- 7.5 mm Hg
- Index TAVR residual gradient was 11.1 mmHg
REDO TAVR OUTCOMES

![Graph showing outcomes](image)

- Mortality
- High Residual Gradient (>20 mmHg)
- AI (>moderate)
- Coronary Obstruction
- New PPM

Incidence, %

- All Patients
- Procedure Failure
- Prosthesis Failure

Landes U, JACC 2020

REDO TAVR VALVE PERFORMANCE

![Performance chart](image)

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Residual Gradient</th>
<th>Coronary Flow Obstruction</th>
<th>Mortality at 30 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failed TAVR Valve</td>
<td>0.22%</td>
<td>13 mm Hg</td>
<td>0.7%</td>
</tr>
<tr>
<td>Failed TAVR Procedure</td>
<td>0.11%</td>
<td>11.5 mm Hg</td>
<td>1.3%</td>
</tr>
</tbody>
</table>

Landes U, JACC 2020
HOW DOES THAT COMPARE TO TAVR IN SAVR?

REDO TAVR VS TAVR IN SAVR

Transcatheter Aortic Valve Implantation in Transcatheter Aortic Valve (TAV-in-TAV) 37 centers, n = 434

Exclusion: • 223 patients with single procedure

TAV-in-TAV n = 212

Transcatheter Aortic Valve Implantation in Surgical Aortic Valve (TAV-in-SAV) 13 centers, n = 624

Exclusion: • 29 patients with missing data

TAV-in-SAV n = 595

Propensity score matching

TAV-in-TAV n = 165

TAV-in-SAV n = 165

Landes U, JACC 2021
REDO TAVR VS TAVR IN SAVR

Landes U, JACC 2021

REDO TAVR VS TAVR IN SAVR

Landes U, JACC 2021

MHIF Cardiovascular Grand Rounds | April 19, 2021
CONCLUSION: TAVR IN TAVR APPEARS TO BE SAFE!
IS THAT THE FULL STORY?!

LIMITATIONS OF REDO TAVR REGISTRY

• The denominator is missing
• Only low risk patients are offered TAVR in TAVR
• What about patients who have TAVR dysfunction and were not candidate for redo TAVR?
TAVR IN TAVR PLANNING

TAVR IN TAVR IS AN ART

- Maintain coronary perfusion
- Maintain coronary access
- Choosing/positioning the second valve
- Avoid patient prosthesis mismatch
CAD IN TAVR PATIENTS IN CLINICAL TRAILS

- About 50% of TAVR patients have CAD
- 11% have LM disease
- 50% have LAD disease
- About 10% will present with ACS within 2 years
- Success rate of PCI is only 90% in those with Corevalve


Screening and Procedural Considerations

<table>
<thead>
<tr>
<th>Original THV Design</th>
<th>Original THC Characteristics</th>
<th>Anatomy</th>
<th>Failure Mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td>THV position in native anatomy</td>
<td>Coronary Access</td>
<td>PVL – malposition / calcification / size</td>
</tr>
<tr>
<td>Size</td>
<td>Expansion shape and ID/OD</td>
<td>Calcifications</td>
<td>Denegation – stenosis vs regurgitation</td>
</tr>
<tr>
<td>Frame design</td>
<td>Commissure Alignment</td>
<td>Sinus / VTC</td>
<td>Leaflet thrombosis</td>
</tr>
<tr>
<td>Leaflet Attachment</td>
<td>STJ diameter and Sinus Heights</td>
<td>Room to expand original THV</td>
<td></td>
</tr>
</tbody>
</table>
KEY TERMINOLOGY

• **Commissure** – Leaflet outflow attachment
• **Valve To Coronary**: distance measured from the valve to coronary ostia
• **Risk Plane**
• **Valve To Aorta (VTA) or Valve To STJ**: Distance between the valve stent frame to the aorta or STJ

RISK PLANE

• Level at which the stent frame of the first THV will be covered after the leaflets are displaced vertically with the implantation of the second THV

**THV in THV ➔ Large covered stent!**
SAPIEN IN EVOLUT

Outflow Orientation

Constrained Portion
Valve Function
Area of Valve Dysfunction

Inflow Portion
Sealing

Need to be covered by the new valve

25 – 30 mm

PATIENT RELATED FACTORS

STJ Height

Coronary Height

STJ Dimension

Sinus of Valsalva Dimensions
VALVE – PATIENT INTERPLAY

Possible scenarios

VALVE PATIENT INTERPLAY – SCENARIO #1

Coronary Artery ABOVE Risk Plane

THV in THV is likely feasible
### Valve Patient Interplay – Scenario #2

- **Coronary Artery BELOW Risk Plane**
- **Large VTA distance / Valve Bellow STJ**
- **THV in THV is likely feasible**

### Valve Patient Interplay – Scenario #3

- **Coronary Artery BELOW Risk Plane**
- **Small VTA distance**
- **Sinus Sequestration!**
- **THV in THV is likely NOT feasible**
PLANNING SECOND VALVE
VIRTUAL CT ANALYSIS
LOW RISK TRIAL

- Sapien valve
- Enrolled 200 subjects
- 137 subjects had 30-day CTA + adequate image quality for analysis
- Age: mean 74 years
- Comprehensive CTA assessment

Rogers, T, et al, JACC Intv 2020
THE COREVALVE EVOLUT PRO PROSPECTIVE REGISTRY (EPROMPT; NCT03423459)

- 81 patients had Evolut/ Corevalve
- CTA was performed 30 days after TAVR
EVOLUT IN EVOLUT EXAMPLE
THE COREVALVE EVOLUT PRO PROSPECTIVE REGISTRY (EPROMPT; NCT03423459)

WHAT THE STUDY ADDS
Our computed tomography–based simulation predicts the following:
• There is a risk of coronary obstruction due to sinus sequestration after TAVR-in-TAVR with an Evolut PRO or Evolut PRO+ transcatheter heart valve in up to 1 in 4 patients.
• Future coronary access is likely to be not possible, or exceedingly challenging, in up to 4 of 5 patients after TAVR-in-TAVR.

Forrestal, et al, CIRC Intv 2020

THE RESOLVE REGISTRY (CEDARS-SINAI)

• Virtual analysis of Post-TAVR CT
  • 66 patients ➔ Evolut R or Evolut PRO
  • 345 patients ➔ Sapien S3

• Sinus Sequestration:
  • Prior TAV commissure level was above sinotubular junction (STJ)
  • The distance between TAV and STJ was <2.0 mm in each coronary sinus

Makkar, et al, JACC Intv 2020
**FIGURE 1** Mechanism of Coronary Obstruction Due to Sinus Sequestration in Redo TAVR and Definition of the CT-identified Risk

A

**Mechanism of Coronary Obstruction Due to Sinus Sequestration in Redo TAVR**

- Evolut R/Evolut PRO
- SAPIEN 3
- Sinus Sequestration

- First TAV Commisural Level
- First TAV Leaflets
- Evolut R/Evolut PRO Commisural Posts
- SAPIEN 3 Commisural Posts

**FIGURE 2** CT Measurements

<table>
<thead>
<tr>
<th>Measurement</th>
<th>LCS</th>
<th>RCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>The distance from the inflow of TAV to STJ in each coronary sinus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STJ in LCS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STJ in RCS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The distance from the inflow of TAV to STJ in LCS = 29.0 mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The distance from the inflow of TAV to STJ in RCS = 30.4 mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The distance between TAV and STJ in LCS = 1.6 mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The distance between TAV and STJ in RCS = 4.6 mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The angle between TAV commissures and each coronary cleft</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The angle between the LCA cleft and the nearest TAV commissure = 30°</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The angle between the RCA cleft and the nearest TAV commissure = 45°</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The overlap between the LCA cleft and the TAV commissural post</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Representation Case of CT-identified Risk of Coronary Obstruction Due to Sinus Sequestration**

- First TAV commissure level > STJ level in both LCS and RCS

- The distance between TAV and STJ = 3.8 mm in both LCS and RCS

- The distance between TAV and STJ = 2.8 mm in both LCS and RCS
The RESOLVE Registry (Cedars-Sinai)

**Figure 3**: CT-identified Risk of Sinus Re-segmentation in Native TAVR vs Evolut R/Evolut PRO and SAPDEN 3

- LCA: **14.4** (Prior Evolut R/Evolut PRO) vs **16.4** (Prior SAPDEN 3), *P = 0.001*
- RCA: **24.2** (Prior Evolut R/Evolut PRO) vs **24.6** (Prior SAPDEN 3), *P = 0.001*
- Both: **16.0** (Prior Evolut R/Evolut PRO) vs **16.0** (Prior SAPDEN 3)
- 1 or Both: **45.1** (Prior Evolut R/Evolut PRO) vs **16.0** (Prior SAPDEN 3), *P = 0.001*

CT-identified risk of sinus re-segmentation in native TAVR vs Evolut R/Evolut PRO and prior SAPDEN 3 is shown. Abbreviations as in Figure 5.

PLANNING FEASIBLE PATIENTS REMAINS A CHALLENGE
VALVE SIZING – MANY UNKNOWNS

• Same index valve size if using the same brand?
  • 1st valve expansion
• Should we size based on native anulus?
• Should we use ViV APP?

VALVE SIZING – AVOID PINWHEELING
VALVE SIZING

- No data available for valve sizing for Accurate Neo, Medtronic, or Portico valve
Valve Positioning

• Very limited data
• More straightforward when using same brand
• More challenging when the index valve is self-expandable

REPEAT TAVR AND IMPLICATIONS FOR THV PERFORMANCE: INSIGHTS FROM BENCH TESTING

Index Valve

2nd Valve

Outcome

Sapien 3, Evolut Pro, Acurate neo, Allegra, and Portico

Hydrodynamic function was evaluated using a pulse duplicator
Multimodality imaging was performed

Sathananthan et al. Eurointervention 2021
Index Valve
23 mm Sapien XT
WHAT ABOUT HIGH RISK PATIENTS?
ROLE OF CORONARY PROTECTION!

CORONARY PROTECTION

BASILICA

CHIMNEY STENT
CHIMNEY STENTING

### Table 6: 30-Day Clinical Outcomes (N = 60)

<table>
<thead>
<tr>
<th></th>
<th>CAD</th>
<th>Coronary Protection</th>
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<tbody>
<tr>
<td></td>
<td>Total (N = 60)</td>
<td>CAD (n = 56)</td>
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<tr>
<td></td>
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</tr>
<tr>
<td></td>
<td>Procedural death</td>
<td>3 (5.0)</td>
</tr>
<tr>
<td></td>
<td>30-day death</td>
<td>3 (5.0)</td>
</tr>
<tr>
<td></td>
<td>MACE</td>
<td>12 (20.0)</td>
</tr>
<tr>
<td></td>
<td>Cardiogenic shock</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td></td>
<td>Major vascular complication</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td></td>
<td>Left Main / Chordal Stenting</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td></td>
<td>AKI grade 3</td>
<td>3 (5.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 (1.7)</td>
</tr>
</tbody>
</table>

Values are n (%) for CAD = coronary artery disease, MACE = major adverse cardiovascular events, AKI = acute kidney injury.

![Central Illustration: Chimney Stenting Procedural Steps](image)

**Step 1:** An uncoiled coronary stent, appropriately sized for the size of the left main coronary artery, is deployed into the ascending aorta to the level of the sinus of Valsalva. A guidewire is inserted into the coronary ostium before transcather heart valve (THV) deployment. **Step 2:** During THV implantation, the guide catheter is locked into the ascending aorta. **Step 3:** If coronary blood flow is compromised, a distal filter is removed and the THV is deployed into the left main coronary artery. **Step 4:** If post-dilation of the THV is required, simultaneous kissing balloon inflation can be performed between the THV and chimney stent to avoid deformation of the chimney stent. **Step 5:** If final angiographic assessment is mandatory, THV = transcather heart valve replacement.

BASILICA

224 patients from 25 centers at risk of coronary artery obstruction during TAVR

On exit from the catheterization laboratory:
- 94.4% Successful BASILICA traversal and laceration
- 86.9% successful BASILICA without coronary obstruction, mortality/re-intervention
- 4.7% partial or complete coronary obstruction

At 30 days (n = 214):
- 2.8% Mortality
- 2.8% stroke
- 0.5% disabling stroke

Khan, JACC-Interventional 3/2021
COMMISSURES, SKIRTS AND BASILICA

- Splay Angles and slit width
  - Sapien XT & Lotus > Sapien 3 and Evolut R

We believe that BASILICA may NOT reliably prevent coronary obstruction for TAVR in-TAVR, especially when the predicted mechanism of obstruction is sinus of Valsalva effacement.
BACK TO OUR CASE!

CARDIAC CTA
TAVR 2020 – EVOLUT PRO 23 MM

• TTE next day:
  • Mean gradient 16-17 mmHg
  • Mild PVL

LETS GO TO THE FUTURE!
CONCLUSION

- TAVR is feasible in selected patients
- Specific consideration 1<sup>st</sup> THV selection and positioning is important in allowing future TAVR in TAVR
- Coronary protection techniques might be helpful, but still limited
TAVR MANAGEMENT IS A LIFETIME JOURNEY

Thanks!