Fifteen Years After the First TAVR, Where Are We and Where Are We Headed?

Martin B. Leon, MD

Columbia University Medical Center
Cardiovascular Research Foundation
New York City

CACI in Partnership with TCT: 40 Years of Interventional Cardiology
Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

<table>
<thead>
<tr>
<th>Affiliation / Financial Relationship</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grant / Research Support</td>
<td>Abbott, Boston Scientific, Edwards Lifescience, Medtronic</td>
</tr>
<tr>
<td>Consulting Fees / Honoraria</td>
<td>Abbott, Boston Scientific</td>
</tr>
<tr>
<td>Shareholder / Equity</td>
<td>Cathworks, Claret, Elixir, GDS, Medinol, Mitralign, Valve Medical</td>
</tr>
</tbody>
</table>
TAVR in Perspective

History
TAVR in Perspective

**History**

- The “proof-of-concept” first TAVI case performed by Alain Cribier and his team in Rouen, FR deserves special attention on this 15th year anniversary!
Antegrade Approach: Guidewire Position in LV
Valve Positioning
April 16, 2002; FIM-TAVI, Transseptal
April 16, 2002; FIM-TAVI, Transseptal
April 16, 2002; FIM-TAVI, Transseptal

15 min Post-TAVI
TAVR in Perspective

Current Role
TAVR in Perspective

Current Role

- Explosive growth in TAVR worldwide
Estimated Global TAVR Growth

This year > 100,000 and by 2025 almost 300,000!

SOURCE: Credit Suisse TAVI Comment – January 8, 2015. ASP assumption for 2024 and 2025 based on analyst model. Revenue split assumption in 2025 is 45% U.S., 35% EU, 10% Japan, 10% ROW
TAVR in Perspective

Current Role

• Explosive growth in TAVR worldwide

“Drivers” of TAVR Growth

1. commitment to evidence-based medicine
2. rapid technology advancement
3. simplification of the procedure
4. striking reduction in complications
Since 2007, in the U.S., > 15,000 patients have been enrolled in FDA studies (including 10 RCTs) with multiple generations of four different TAVR systems!
TAVR Newcomers

Global Landscape (#25)

Current Leaders!
- Sapien 3
- Evolut R
- Lotus

Future Contenders?
- J – Valve Ausper
- VitaFlow (Microport)
- Taurus One
- Trinity
- Centera
- Venus A Valve

- HLT Meridian
- NVT (Nautilus)
- Xeltis
- Zurich TEHV
TAVR Accessory Devices

Cerebral Embolic Protection (CEP)

- Dual, independent filter (proximal and distal)
- Cerebral embolic protection device with visible embolic debris capture and removal
- The 3rd generation CE-marked embolic protection device
- Universal size and shape
- Deflectable compound curve sheath facilitates cannulation of LCC
- Right transradial 6F sheath access using a standard 0.014" guidewire
- Filters are out of the way of TAVI delivery catheter and accessories during the TAVI procedure

Proximal Filter (Innominate Artery) 9–15 mm

Distal Filter (LCC Artery) 6.5–10 mm
The Minimalist Strategy

- No general anesthesia; use “conscious sedation”
- >70% of TAVR cases worldwide are good candidates for a “minimalist” procedural strategy!
- Median LOS after TAVR is 2 days at Columbia-NYP Hospital!
- No ICUs... monitor in recovery area
- Rapid ambulation and early discharge plans (1-2 dys)
All-Cause Mortality at 30 Days
Edwards SAPIEN Valves (As Treated)

PARTNER 1 and 2 Trials
(Overall and TF Patients)
PARTNER 1 and 2 Trials
(Overall and TF Patients)

Neurologist evaluations (pre- and post)

<table>
<thead>
<tr>
<th>Group</th>
<th>Pre-Percent</th>
<th>Post-Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAPIEN</td>
<td>6.7%</td>
<td>4.1%</td>
</tr>
<tr>
<td>SAPIEN XT</td>
<td>5.6%</td>
<td>4.3%</td>
</tr>
<tr>
<td>SAPIEN 3</td>
<td>1.5%</td>
<td>2.6%</td>
</tr>
</tbody>
</table>

Strokes (All) at 30 Days
Edwards SAPIEN Valves
PARTNER I and II Trials
Overall and TF Patients

Moderate/Severe PVL at 30 Days
Edwards SAPIEN Valves

<table>
<thead>
<tr>
<th>Trial</th>
<th>SAPIEN</th>
<th>SAPIEN XT</th>
<th>SAPIEN 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1B (TF)</td>
<td>12.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P1A (Overall)</td>
<td>11.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P2B (TF)</td>
<td>16.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P2B XT (TF)</td>
<td>24.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S3HR (Overall)</td>
<td>2.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S3i (Overall)</td>
<td>4.2%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

179 344 276 284 583 1076
TAVR in Perspective

**Current Role**

- Explosive growth in TAVR worldwide
- Evolving recommended use guidelines and expansion of clinical indications
TAVR Guidelines

The “New” AHA/ACC Focused Update

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

Severe AS Symptomatic

Surgical Risk Strata

Low: SAVR

Intermediate: SAVR or TAVR

High: SAVR or TAVR

Prohibitive: TAVR

IB

Ila B

IA

IA
TAVR Guidelines
The “New” ESC/EACTS VHD Report

2017 ESC/EACTS Guidelines for the management of valvular heart disease
The Task Force for the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

Severe AS Symptomatic

Surgical Risk Strata

Low

Intermediate or High

Prohibitive

SAVR

SAVR or TAVR

TAVR
TAVR Risk Assessment

Risk Stratification Redefined

Traditional

Low  Intermediate  High  Extreme/Inoperable

Contemporary

Lower risk  Higher risk

Courtesy of N. Piazza
Expanding TAVR Clinical Indications

A Transformative Technology at the Crossroads?

• Bioprosthetic aortic valve failure
• Low-risk patients (? all-comers)
• Low-flow, low-gradient AS
• Bicuspid AV disease
• AS + concomitant disease (CAD, MR, AF)
• Severe asymptomatic AS
• Moderate AS + CHF
• High-risk AR
TAVR for Bioprosthetic Valve Failure

Valve-in-Valve

Transcatheter Aortic Valve Implantation
Within Degenerated Aortic
Surgical Bioprostheses

PARTNER 2 Valve-in-Valve Registry

John G. Webb, MD, Michael J. Mack, MD, Jonathon M. White, MD, Danny Dvir, MD, Philipp Blanke, MD, Howard C. Herrmann, MD, Jonathon Leipsic, MD, Susheel K. Kodali, MD, Raj Makkar, MD, D. Craig Miller, MD, Philippe Pibarot, DVM, PhD, Augusto Pichard, MD, Lowell F. Satler, MD, Lars Svensson, MD, PhD, Maria C. Alu, MS, Rakesh M. Suri, MD, DPhil, Martin B. Leon, MD

- 365 high-risk patients with aortic bioprosthesis failure treated with TAVR
- 30-day and 1-yr all-cause mortality was 2.7% and 12.4% respectively

Webb JG et al. JACC 2017;69:2253-62
TAVR in Perspective

Current Role

• Explosive growth in TAVR worldwide
• Evolving recommended use guidelines and expansion of clinical indications
• The Heart Team is now the central vehicle for managing patients with complex valve disease
TAVR in Perspective

**Current Role**

- Explosive growth in TAVR worldwide
- Evolving recommended use guidelines and expansion of clinical indications
- The Heart Team is now the central vehicle for managing patients with complex valve disease
- Acceptance of multi-modality imaging for diagnosis, therapy guidance, and FU
TAVR Accessory Devices

Novel Imaging Systems

Multi-modality Imaging is the RULE!

Patient Follow-up

Patient Screening, Procedural Planning

Intra-procedural Guidance

Angio

CTA

TTE

TEE + 3D
TAVR in Perspective

The Future
TAVR in Perspective

The Future

• Improved disease awareness and access to TAVR (esp. underserved populations)
AS Based on Surgical Experience

2015 Severe Symptomatic AS Patients in the U.S.\(^1\)

AS Including the TAVR Experience

2015 Severe Symptomatic AS Patients in the U.S.¹

AS Patients Undiagnosed and Untreated

2015 Severe Symptomatic AS Patients in the U.S.¹

TAVR in Perspective

The Future

• Improved disease awareness and access to TAVR (esp. underserved populations)
• Further innovation of TAVR platforms (e.g. tissue engineered heat valves)
Zurich Tissue Engineered Heart Valve

A “Living” Aortic Valve

Courtesy of Simon P. Hoerstrup, MD, PhD
Xeltis

Endogenous Tissue Restoration (ETR)

- Synthetic matrix made of novel bioborbable supramolecular polymers using electrospinning techniques
- Polymer leaflets mounted on nitinol self-expanding frame
- Regrowth of endogenous tissue coincident with bioabsorption of polymer implant
- Natural self-healing anti-inflammatory leaflets

Valve after bioabsorption
Xeltis
Endogenous Tissue Restoration (ETR)

- Synthetic matrix made of novel bioborbable supramolecular polymers using electrospinning techniques
- Polymer leaflets mounted on nitinol self-expanding frame
- Regrowth of endogenous tissue coincident with bioabsorption of polymer implant
- Natural self-healing anti-inflammatory leaflets
TAVR in Perspective

The Future

- Improved disease awareness and access to TAVR (esp. underserved populations)
- Further innovation of TAVR platforms (e.g. tissue engineered heat valves)
- Realization of ‘completely’ new clinical indications for TAVR - leveraging the advantages of less-invasive Rx
Asymptomatic Severe AS and 2D-TTE (PV ≥4m/s or AVA ≤1 cm²)
Exclusion if patient is symptomatic, EF<50%, concomitant surgical indications, bicuspid valve, or STS >8

Treadmill Stress-Test

Stress-Test Normal
- CTA and Angiography
  - TF- TAVR eligibility
- Early-TAVR Randomized Trial

Stress-Test Abnormal
- TF- TAVR
- Clinical Surveillance
- Early TAVR Registry

Randomization 1:1
Stratified by STS (<3 vs ≥3)

Primary Endpoint (superiority): 2-year composite of all-cause mortality, all strokes, and repeat hospitalizations (CV)
Heart Failure
LVEF < 50%
NYHA ≥ 2
Optimal HF therapy (OHFT)
Moderate AS

TAVR UNLOAD Trial
Study Design
(600 patients, 1:1 Randomized)

Follow-up:
1 month
6 months
1 year
Clinical endpoints
Symptoms
Echo
QoL

Primary Endpoint
Hierarchical occurrence of:
- All-cause death
- Disabling stroke
- Hospitalizations for HF, aortic valve disease
- Change in KCCQ

TAVR + OHFT
OHFT Alone

Reduced AFTERLOAD
Improved LV systolic and diastolic function

TAVR UNLOAD Trial
International Multicenter Randomized
TAVR in Perspective

The Future

- Re-defining AS disease classification, pathophysiology, and “trigger points” for intervention
Staging classification of aortic stenosis based on the extent of cardiac damage

Philippe Généreux\textsuperscript{1,2,3}, Philippe Pibarot\textsuperscript{4}, Björn Redfors\textsuperscript{1,5}, Michael J. Mack\textsuperscript{6}, Raj R. Makkar\textsuperscript{7}, Wael A. Jaber\textsuperscript{8}, Lars G. Svensson\textsuperscript{8}, Samir Kapadia\textsuperscript{8}, E. Murat Tuzcu\textsuperscript{8}, Vinod H. Thourani\textsuperscript{9}, Vasilis Babaliaros\textsuperscript{9}, Howard C. Herrmann\textsuperscript{10}, Wilson Y. Szeto\textsuperscript{10}, David J. Cohen\textsuperscript{11}, Brian R. Lindman\textsuperscript{12}, Thomas McAndrew\textsuperscript{1}, Maria C. Alu\textsuperscript{13},

<table>
<thead>
<tr>
<th>Stages/Criteria</th>
<th>Stage 0</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Cardiac Damage</td>
<td>LV Damage</td>
<td>LA or Mitral Damage</td>
<td>Pulmonary Vasculature or Tricuspid Damage</td>
<td>RV Damage</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>Increased LV Mass Index $&gt;115$ g/m$^2$ (Male)</td>
<td>Indexed left atrial volume $&gt;34$ mL/m$^2$</td>
<td>Systolic Pulmonary hypertension $&gt;60$ mmHg</td>
<td>Moderate-Severe right ventricular dysfunction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$&gt;95$ g/m$^2$ (Female)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$E/e'$ $&gt;14$</td>
<td>Moderate-Severe mitral regurgitation</td>
<td>Moderate-Severe tricuspid regurgitation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>LV Ejection Fraction $&lt;50%$</td>
<td>Attral Fibrillation</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

tct2017

Columbia University Medical Center

NewYork-Presbyterian
Staging classification of aortic stenosis based on the extent of cardiac damage

**Number at risk:**

- Stage 4: 24.5%
- Stage 3: 21.3%
- Stage 2: 14.4%
- Stage 1: 9.2%
- Stage 0: 4.4%

*p<0.0001*
LMP → Ventricular Load

PWA → Vascular State

MIT - CRF Collaboration

Enhanced Prediction Models
- Predict who will better benefit from TAVR
- Decide when is the best timing of intervention

Refine characterization of CV dynamics to enable

Redefine the Pathophysiology
TAVR in Perspective

The Future

• Re-defining AS disease classification, pathophysiology, and “trigger points” for intervention

• There are still important knowledge gaps with TAVR which must be resolved (esp. valve leaflet thickening & thrombosis, durability, and optimal adjunctive pharmacotherapy)
Valve Leaflet Abnormalities

Makkar, et al. NEJM 2015
All TAVR systems will certainly demonstrate evidence of valve degeneration during long-term (> 5 years) assessments, especially if echo criteria are applied in the definitions of durability!

Surgically explanted Sapien and CorveValve THVs
New EU guidance with standardized definitions and endpoints to assess bioprosthetic aortic valve deterioration and failure.
# TAVR Adjunct Pharmacology

## Customized Patient-Based Therapy

<table>
<thead>
<tr>
<th>BEFORE</th>
<th>DURING</th>
<th>AFTER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylsalicylic acid (ASA)</td>
<td><strong>UNFRACTIONATED HEPARIN:</strong> target ACT $\geq 300^\circ$</td>
<td>ASA + CLOPIDOGREL</td>
</tr>
<tr>
<td></td>
<td><strong>Bivalirudin:</strong></td>
<td>Acetylsalicylic acid (ASA) ARTE trial</td>
</tr>
<tr>
<td></td>
<td><strong>Low Molecular Weight Heparin</strong></td>
<td>Non anti-VKA Oral Anticoagulant ± ASA:</td>
</tr>
</tbody>
</table>

*Image credits: [Columbia University Medical Center](https://www.columbia.edu/), [TCT 2017](https://www.tct.org/)*
TAVR is a breakthrough therapy for our patients!

92 yo man with critical AS...#1 TAVR at Columbia-NYP

- severe COPD
- creat 2.8
- previous CABG (patent LIMA)
- EF 30%
- Class IV CHF
- STS 15.5%