TAVR in Perspective: Evolution, Impact, and Future Expectations

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10 mins
Disclosure Statement of Financial Interest
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Martin B. Leon, MD

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>
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<tr>
<td>Grant / Research Support</td>
<td>Abbott, Boston Scientific, Edwards Lifescience, Medtronic,</td>
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<td>Consulting Fees / Honoraria</td>
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<td>Shareholder / Equity</td>
<td>Claret, GDS, Mitralign, Valve Medical</td>
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</table>
TAVR in Perspective

Evolution
TAVR in Perspective

Historical Context

• 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!
Valve Positioning
April 16, 2002; FIM-TAVI, Transseptal

Valve Deployment
April 16, 2002; FIM-TAVI, Transseptal

15 min Post-TAVI
TAVR in Perspective

**Historical Context**

- 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!

- There is a rich history of many other key individuals who have also contributed to the development of TAVR and should be recognized.
TAVR in Perspective

**Early TAVR Pioneers**

- Hening Rud Andersen -
  1989: *First porcine implant*

- Philipp Bonhoeffer -
  2000: *First human implant (RV to PA conduit)*
Collaboration across the seas....

Drs. John Webb and Alain Cribier
The Heart Team - A Deal with the Devil?

Transapical case

M. Mack

Leipzig 2004

F. Mohr
TAVR in Perspective

Early TAVR Pioneers

- Eberhard Grube -

2004

- Jacques Seguin -

Design concepts and clinical FIM experiences with self-expanding THVs
1985

« Percutaneous Valve Technology » (prototypes)

1994

Post-mortem studies of intra-valvular stenting

1999

Feasibility Studies (antegrade)

2000

Animal implantations (sheep)

2002

F.I.M. Balloon Aortic Valvuloplasty

2002-03

Edwards Lifesciences TF & TA Feasibility Studies

2004

F.I.M. THV implantation

2005-07

International TF and TA Feasibility Studies

2007

Since 2007

CoreValve

US Pivotal Trials

Registries

CE Mark

FIM

Oct 2011- FDA Approval: Non Surgical Patients (PARTNER B)

Oct 2012- FDA Approval: High Risks Patients (PARTNER A)

CE mark commercialization

Post market registries

CoreValve

Oct 2011 - FDA Approval: Non Surgical Patients (PARTNER B)

Oct 2012- FDA Approval: High Risks Patients (PARTNER A)
TAVR in Perspective

Drivers of Success

• The Multi-disciplinary Heart Team
• Commitment to Evidence-Based Medicine
TAVR in Perspective

The VARC Process

Standardized Endpoint Definitions for Transcatheter Aortic Valve Implantation

Updated Standardized Endpoint Definitions for Transcatheter Aortic Valve Implantation

The Valve Academic Research Consortium-2 Consensus Document†


Rotterdam, the Netherlands
TAVR in Perspective

STS database 2002-2010 (141,905 pts)

Since 2007, in the U.S., >15,000 patients have been enrolled in FDA studies (including 8 RCTs) with multiple generations of two TAVR systems!
Pipeline of TAVR Trials across the spectrum of aortic stenosis

**Published**
- 2010
- 2011
- 2012
- 2013
- 2014
- 2015
- 2016
- 2017

**Upcoming**
- 2017
- 2018
- 2019
- 2020
- 2021

**AS with no symptoms**

<table>
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<tr>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
<th>Extreme</th>
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<tr>
<td>2010</td>
<td>PARTNER 1A</td>
<td>Corevalve US HR</td>
<td>PARTNER 1B</td>
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<tr>
<td>2014</td>
<td>NOTION</td>
<td>PARTNER 2A</td>
<td>PARTNER 2B</td>
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<td>2016</td>
<td>PARTNER 2 S3</td>
<td>PARTNER 2 S3i</td>
<td>SURTAVI</td>
</tr>
<tr>
<td>2017</td>
<td>PARTNER 3</td>
<td>US Evolut R LR</td>
<td>UK TAVI</td>
</tr>
<tr>
<td>2018</td>
<td>PARTNER 3</td>
<td>REBOOT</td>
<td>REPRISE 3</td>
</tr>
<tr>
<td>2019</td>
<td>PARTNER 3</td>
<td>SALUS (stopped)</td>
<td>PORTICO IDE</td>
</tr>
<tr>
<td>2020</td>
<td>NOTION 2</td>
<td>SOLVE-TAV</td>
<td>SCOPE 1</td>
</tr>
<tr>
<td>2021</td>
<td>EARLY TAVR</td>
<td>TAVR UNLOAD</td>
<td>SCOPE 2</td>
</tr>
</tbody>
</table>

**Investigational devices**
- Edwards Sapien/Sapien XT/S3
- Medtronic CoreValve/Evolut R
- Boston Lotus
- Direct Flow Medical Direct Flow
- Abbott Vascular Portico
- Symetis Acurate Neo
- Any available TAVR system

24 TAVR RCTs

Capodanno D, Leon MB. EuroIntervention 2016
TAVR in Perspective

Drivers of Success

- The Multi-disciplinary Heart Team
- Commitment to Evidence-Based Medicine
- Rapid Technology Enhancement
TAVR Systems

Global Inventory (#25)

Current Leaders!
• Sapien 3
• Evolut R
• Symetis
• Lotus
• Portico
• Direct Flow
• Engager
• Jena Valve
• Centera
• Venus A Valve

Future Contenders?
• Shanghai Valve
• Trinity
• Colibri
• Incisive
• Thubrikar
• Valve Medical
• Syntheon Verso
• Triskele
• BioValve
• MyVal
• HLT
• NVT (Nautilus)
• J - Valve
• Xeltis
• Zurich TEHV
Trans-Caval Access for TAVR

(202 pts in 28 centers - 5/14/16)
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
TAVR in Perspective

Drivers of Success

- The Multi-disciplinary Heart Team
- Commitment to Evidence-Based Medicine
- Rapid Technology Enhancement
- Simplification of the Procedure
“Outpatient” Same-Day TAVR
Sacre-Coeur Hospital; Montreal, CN

Featured Case Reports

Same Day Discharge after Transcatheter Aortic Valve Replacement: Are We There yet?

Philippe Généreux,1,2* MD, Philippe Demers,1 MD, and Frédéric Poulin,1 MD

Early discharge after transcatheter aortic valve replacement (TAVR) has been increasingly reported, and is now becoming routinely performed in experienced TAVR centers. However, to the best of our knowledge, no case has been described where a patient was safely discharged on the same the day of the procedure. This report will present the case of a patient who underwent a successful transfemoral TAVR and was safely discharged home the same day. Specific requirements and criteria are proposed to ensure the safety of this approach.

Key words: TAVR; TAVI; discharge
TAVR in Perspective

Drivers of Success

• The Multi-disciplinary Heart Team
• Commitment to Evidence-Based Medicine
• Rapid Technology Enhancement
• Simplification of the Procedure
• Striking Reduction in Complications
TAVR in Perspective

Impact
TAVR in Perspective

Impact

• Explosive growth in TAVR worldwide
Estimated Global TAVR Growth

In the next 10 years, TAVR growth will increase X4!

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

**Impact**

- Explosive growth in TAVR worldwide
- Evolving recommended use guidelines
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 (stage D)
- Low surgical risk: Surgical AVR (Class I)
- Intermediate surgical risk: Surgical AVR (Class I)
- High surgical risk: TAVR (Class IIa) or Surgical AVR (Class I)
- Prohibitive surgical risk: TAVR (Class I)
TAVR in Perspective

Impact

• Explosive growth in TAVR worldwide
• Evolving recommended use guidelines
• The Heart Team is now the preferred model for managing complex CV diseases
The Heart Team and Shared Decision-Making

A Call for an Evidence-Based Approach to the Heart Team for Patients With Severe Aortic Stenosis

Megan Coylewright, MD, MPH,* Michael J. Mack, MD,† David R. Holmes, Jr, MD,‡ Patrick T. O’Gara, MD§

ABSTRACT

Application of a Heart Team approach is now a central concept in the care of patients with severe aortic stenosis. It has Class I recommendations from American and European professional societies and is required for reimbursement for transcatheter aortic valve replacement in the United States. The rationale for changing traditional practice models is to improve patient selection, procedural planning, and management of patients at high or prohibitive surgical risk, thus improving outcomes. Although the concept is intuitive, a clear definition of the Heart Team, and data supporting its effectiveness, are lacking. Other specialties, including oncology, provide a precedent for investigation of the use of a multidisciplinary team and its impact on patient care. We highlight the need for clear definitions and shared metrics to advance our understanding of an optimal Heart Team approach, focusing on patient, clinician, and health system outcomes. (J Am Coll Cardiol 2015;65:1472-80) © 2015 by the American College of Cardiology Foundation.

Coylewright M, et al. JACC 2015
TAVR in Perspective

Impact

• Explosive growth in TAVR worldwide
• Evolving recommended use guidelines
• The Heart Team is now the preferred model for managing complex CV diseases
• Carry-over effects = creation of a new subspecialty - Structural Heart Disease
New market segments may exceed PCI market size by 2020
Emergence of future segments relies on technology and clinical data
OUS markets will lead and exceed the size of US markets

Structural Heart Disease:
- All Transcatheter Valves (AS, MR, TR)
- LAA Occlusion
- Heart Failure

Future Segment CAGR
2010 – 2020 = 30%

Existing PCI CAGR
2010 – 2020 = 1-3%
Transcatheter MV Repair: Device Landscape 2017

**Edge-to-edge**
- MitraClip***
- MitraFlex

**Coronary sinus annuloplasty**
- Cardiac Dimensions Carillon**
- Cerclage annuloplasty

**Direct annuloplasty and basal ventriculoplasty**
- Mitralign TAMR**
- Valtech Cardioband**
- GDS Accucinch*
- Millipede IRIS*
- MVRx ARTO*
- Mardil BACE*
- Mitraspan*
- Valcare Amend*
- Micardia enCor
- Cardiac Implants RDS
- QuantumCor (RF)

**MV replacement**
- Edwards CardiAQ*
- Edwards Fortis*
- Neovasc Tiara*
- Abbott Tendyne*
- Medtronic Intrepid*
- HighLife*
- MValve*
- Caison*
- NCSI NaviGate
- St. Jude
- Micro Interventional
- Valtech CardioValve
- ValveXchange
- MitrAssist
- Braile Quattro
- Cephea
- Direct Flow
- Sinomed Accufit

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

**Other approaches**
- NeoChord DS 1000**
- Harpoon neochords*
- Babic chords*
- Middle Peak Medical*
- St. Jude leaflet plication*
- Cardiosolutions Mitra-Spacer*
- Valtech Vchordal
- Mitralix

*In patients  *CE mark *FDA approved
Structural Heart: The Journal of the Heart Team is the new journal emphasizing the importance of the Heart Team in diagnosing and treating diseases of the heart valves, myocardium, and great vessels, as well as congenital heart disease.

Topics covered include:
• Diagnostic techniques
• Percutaneous interventional procedures
• Cardiovascular surgery
• Drug treatment
• Findings from the laboratory
• Clinical trials

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TAVR in Perspective

**Impact**

- Explosive growth in TAVR worldwide
- Evolving recommended use guidelines
- The Heart Team is now the preferred model for managing complex CV diseases
- Carry-over effects = creation of a new subspecialty - Structural Heart 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

Images:
- Angio
- CTA
- TTE
- TEE + 3D
TAVR in Perspective

Impact

- Explosive growth in TAVR worldwide
- Evolving recommended use guidelines
- The Heart Team is now the preferred model for managing complex CV diseases
- Carry-over effects in the development of a new subspecialty - Structural Heart Disease
- Acceptance of multi-modality imaging for diagnosis, therapy guidance, and FU
- Exploration of new clinical indications
Expanding TAVR Clinical Indications

A Transformative Technology at the Crossroads?

- Bioprosthetic valve failure (aortic and mitral)
- 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 in Perspective

Expectations
TAVR in Perspective

Expectations

• 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

Access to TAVR in the U.S.

28 states with more SAVR-Only sites than TAVR/SAVR sites!

SOURCE: Industry estimates
Access to TAVR in the U.S.

- TAVR site training over the past 5 years in the US has been carefully structured to achieve optimal clinical outcomes; site evolution will plateau over the next several years (≈ 1 TAVR site per 500,00 persons)

- Access to TAVR in the US is still limited and impacted by the distribution of TAVR/SAVR vs. SAVR-only sites
  - currently, there are ≈ 700 SAVR-only sites, accounting for 30% of the SAVR procedures
  - > 55% SAVR performed at SAVR-only sites were at sites > 50 miles from a TAVR program
### Annual TVT Report (2016)

#### Underserved Populations

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<th>Variable</th>
<th>Level</th>
<th>Overall (n=54,782)</th>
<th>2012 (n=4,627)</th>
<th>2013 (n=9,052)</th>
<th>2014 (n=16,295)</th>
<th>2015 (n=24,808)</th>
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<td>Median</td>
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<td>84.0</td>
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<tr>
<td>Gender (%)</td>
<td>Male</td>
<td>51.7</td>
<td>52.6</td>
<td>46.9</td>
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<td>52.7</td>
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<td>Race (%)</td>
<td>White</td>
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<td>94.2</td>
<td>93.8</td>
<td>94.1</td>
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<td></td>
<td>Black/African American</td>
<td>3.8</td>
<td>3.8</td>
<td>3.5</td>
<td>3.9</td>
<td>3.8</td>
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<td></td>
<td>Asian</td>
<td>1.1</td>
<td>1.1</td>
<td>1.3</td>
<td>1.3</td>
<td>1.0</td>
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<tr>
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<td>Hispanic or Latino Ethnicity</td>
<td>3.8</td>
<td>3.5</td>
<td>3.5</td>
<td>3.9</td>
<td>4.0</td>
</tr>
</tbody>
</table>

Despite similar disease prevalence and TAVR treatment outcomes, there are race-based underserved populations with reduced access!
TAVR in Perspective

**Expectations**

- Improved disease awareness and access to TAVR (esp. underserved populations)
- Accelerated innovation of TAVR platforms (e.g. tissue engineered heart 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 biobosorbable 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
TAVR in Perspective

*Expectations*

- Improved disease awareness and access to TAVR (esp. underserved populations)
- Accelerated innovation of TAVR platforms (e.g. tissue engineered heart valves)
- Re-defining AS disease state and “trigger points” for therapy (beyond Braunwald-Ross)
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

**Expectations**

- Improved disease awareness and access to TAVR (esp. underserved populations)
- Accelerated innovation of TAVR platforms (e.g. tissue engineered heart valves)
- Re-defining AS disease state and “trigger points” for therapy (beyond Braunwald-Ross)
- Realization of new clinical indications
TAVR UNLOAD Trial

**Study Design**

(600 patients, 1:1 Randomized)

Heart Failure
LVEF < 50%
NYHA ≥ 2
Optimal HF therapy (OHFT)
Moderate AS

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

Follow-up:
1 month
6 months
1 year

Clinical endpoints
Symptoms
Echo QoL

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TAVR UNLOAD Trial
International Multicenter Randomized

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Echo QoL

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

Reduction in AFTERLOAD
Improved LV systolic and diastolic function
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**
  - Early TAVR Registry

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

- TF- TAVR
- Clinical Surveillance

**Primary Endpoint (superiority):** 2-year composite of all-cause mortality, all strokes, and repeat hospitalizations (CV)
# Aortic Stenosis Redefined: Functional Classification

<table>
<thead>
<tr>
<th>Mild AS</th>
<th>Moderate AS Symptoms -</th>
<th>Moderate AS Symptoms +</th>
<th>Severe AS Symptoms -</th>
<th>Severe AS Symptoms +</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TAVR-UNLOAD</td>
<td>EARLY-TAVR</td>
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<tr>
<td>PARTNERs</td>
<td>Low</td>
<td>Inter</td>
<td>High Ext</td>
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</table>

- **TAVR**
  - Active Surveillance
  - 2017
  - ≈2022

**Courtesy of P. Généreux TVT 2017**
TAVR: A 10-Year Anniversary
One doesn’t discover new lands without consenting to lose sight of the shore for a very long time.

Andre Gide
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%