Disclosure Statement of Financial Interest
NY Transcatheter Valves Symposium; Dec 6, 2018

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>
</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>Boston Scientific, Medtronic, Gore, Meril Lifescience</td>
</tr>
<tr>
<td>Shareholder / Equity</td>
<td>GDS, Mitralign, Valve Medical</td>
</tr>
</tbody>
</table>
Dr. Alain Cribier
First-in-Man PIONEER

OK, What Now?

15 min post-TAVR

April 16, 2002
How it began...
The Andersen Stent-Valve (1989)
The Andersen Stent-Valve (1992)

FOUNDERS

Martin Leon
Alain Cribier
Santon Rowe
Stan Rabinovich

Partner: ARAN Research & Development Ltd.
Percutaneous Valve Technologies PVT (PVT) Early Prototypes

- Different valve configurations
- Different leaflet materials, designs and attachment means
- Extensive hydrodynamic testing

PVT designed the testing equipment and crimping tools
PVT 2000-2002: The Sheep Era

CERA (Centre d’Experimentation et de Recherche Appliquée)  
Institut Monsouris, Paris, France
PVT - Cadaver Heart Study at AFIP
The first case in Rouen
Alain Cribier to Martin Leon, Stan Rowe, Stan Rabinovich, Assaf Bash
April 12, 2002

I have a fascinating case that I would like to discuss with you!

Imminent death
EF 10%
BP 60 mmHg with vasopressors

57 y/o Transeptal BAV performed Intra-LV thrombus

Valve implantation, transseptal approach!

Dilatation of the septum required
Externalization of wire

Highest risk !..

Martin Leon to Alain Cribier
April 12, 2002

You have my complete support to move ahead with the first PVT clinical placement in this desperately ill man.

Snaring the stiff wire is a good idea!

Best operator in the world!

High likelihood of failure but... it just might work and save his life!

IABP?
Antegrade Approach: Guidewire Position in LV
April 16, 2002; FIM-TAVI, Transseptal
April 16, 2002; FIM-TAVI, Transseptal
April 16, 2002; FIM-TAVI, Transseptal

Improvement in trans-vavular gradient!
April 16, 2002; FIM-TAVI, Transseptal

It works !!!
Conclusions: Nonsurgical implantation of a prosthetic heart valve can be successfully achieved with immediate and midterm hemodynamic and clinical improvement.
TAVR - The Early Skeptics

- Strokes
- Aortic rupture
- Coronary occlusion
- Mitral valve injury
- Valve instability – embolization
- Para-valvular regurgitation
- Vascular complications
- Valve durability
- Technical challenges insurmountable

This is a crazy project that will fail!
Key Messages

- After the landmark FIM case by Alain Cribier, the next several years were spent replicating and refining the TAVR procedure in extreme-risk patients (I-REVIVE/RECAST and REVIVAL feasibility registries in EU and US).
Transfemoral Retrograde TAVR

Collaboration across the seas....

Drs. John Webb and Alain Cribier

Vancouver 2004
Trans-apical TAVR

A deal with the devil?

Leipzig 2004

Drs. Michael Mack and Fred Mohr
Where we stand today…
After the landmark FIM case by Alain Cribier, the next several years were spent replicating and refining the TAVR procedure in extreme-risk patients (I-REVIVE/RECAST and REVIVAL feasibility registries in EU and US).

Despite the early success of TAVR in extreme risk patients, no one could have predicted the evolution of TAVR into a mainstream therapy with a profound impact on CV medicine!
Reasons for TAVR Success...

1. Rapid technology evolution
2. Procedural refinements and simplification
3. Avalanche of clinical evidence
4. Heart valve team acceptance
5. Explosive growth worldwide
TF TAVR clearly reigns supreme!

Source: STS/ACC TVT Registry Database. 79,714 records as of Jan 18, 2017
The Minimalist Strategy

➢ No general anesthesia; use “conscious sedation”
➢ No TEE, but available TTE support
➢ Percutaneous TF access with percutaneous closure
➢ Minimize IV lines, no Foley catheters, careful sedation and pain meds
➢ No ICUs...
➢ Monitor in recovery area
➢ Rapid ambulation and early discharge plans (1-2 dys)

Almost all TAVR cases worldwide are now candidates for some version of “minimalist” procedural strategy!

Median LOS after TAVR is 1-2 days at Columbia-NYP Hospital!
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 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. © 2015 Wiley Periodicals, Inc.

Key words: TAVR; TAVI; discharge
### Pipeline of TAVR Trials across the spectrum of aortic stenosis

**AS with no symptoms**

<table>
<thead>
<tr>
<th>Year</th>
<th>Published</th>
<th>AS with no symptoms</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
<th>Extreme</th>
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<tr>
<td>2010</td>
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<tr>
<td>2021</td>
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</tbody>
</table>

**Upcoming**

- **2017**
  - REBOOT
  - CHOICE
  - PARTNER 2
  - PARTNER 3
- **2018**
  - SOLVE
  - Pipeline of TAVR Trials across the spectrum of aortic stenosis
- **2019**
  - SCOPE 1
  - NOTION 3
- **2020**
  - EARLY TAVR
- **2021**
  - NOTION 2

---

**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 RCTs**

[Columbia University Medical Center](https://www.cumc.columbia.edu/

[New York-Presbyterian](https://www.nyp.org/)

**Capodanno D, Leon MB. EuroIntervention 2016**

**tct2018**
The Heart Team 3.0

Who’s Missing?

THE PATIENT

Valve Cardiologist

Structural Interventionalist

CV Anesthesiologist

MD Consultants

Transcatheter Surgeon

Imaging Expert

Heart Failure Specialist

Dedicated Coordinator
Estimated US TAVR Growth

2018 - 2025 the US TAVR Market will Increase 2.5X!

In the US, by 2025, >75% of all AVR will be TAVR!

The VARC initiative set the stage for PARTNER, which arguably became the most successful sequence of clinical trials EVER!
{})
PARTNER Heart Valve Team

(Executive Committee)

Lars Svensson  Craig Miller  Murat Tuzcu
Craig Smith
The PARTNER Trials

> 9,000 patients
PARTNER Publications Office (PPO) as of 11/26/18 (Maria Alu)

Acceptance Rate by Journal

- Published
- Under Review
- Rejected (or Transferred)

Total Manuscripts Published: 100 (23 different journals)
Total Abstracts Presented: 120 (12 distinct scientific symposia)
The VARC initiative set the stage for PARTNER, which arguably became the most successful sequence of clinical trials EVER!

The PARTNER trials and the MDT CoreValve studies applied the highest level of clinical trial rigor, including 8 RCTs, to validate the relative safety and efficacy of TAVR cw control therapies (e.g. medical Rx or surgery) in de-escalating risk strata over a ten-year period!
TAVR Patient Selection

Surgical Risk Stratification

- Low
- Intermediate
- High
- Extreme
TAVR Risk Assessment

Risk Stratification Redefined

Traditional

Low | Intermediate | High | Extreme/Inoperable

Contemporary

Lower risk | Higher risk

Columbia University Medical Center
NewYork-Presbyterian

tct2018
TAVR Risk Assessment

**TAVR Higher-Risk Strata**

**Futility (cohort C)**

- Life expectancy < 1 year, despite successful TAVR
- Risk predictive models for early mortality or poor clinical outcomes with TAVR
- Co-morbidities (STS > 15%)
- Frailty and dementia assessments critical
- \( Rx = BAV \) or hospice
Role of Frailty Assessment

- Robust
- Frail
- Extremely Frail

Frailty Syndrome

- Cachexia
- Severe weakness
- Wheelchair bound
- Dementia
- ADL dependencies

TAVR

Hospice? BAV?

Suzanne Arnold, TCT 2016
TAVR Risk Assessment

TAVR Higher-Risk Strata

Extreme or Prohibitive Risk; “Inoperable”

- > 50% likelihood of death or irreversible morbidity
- Heart team decision with surgeons as the gatekeepers
- Clinical & anatomic exclusions for surgery
- TAVR is only option
All-Cause Mortality (ITT)
All Patients

- Standard Rx (n = 179)
- TAVR (n = 179)

HR [95% CI] = 0.50 [0.39, 0.65]

p (log rank) < 0.0001
All-Cause Mortality (ITT) Median Survival

Standard Therapy: 11.1 Months

TAVR: 29.7 Months

p (log rank) < 0.0001
TAVR Risk Assessment

TAVR Higher-Risk Strata

High Risk

- STS score ≥8%
- Combination of clinical co-morbidities and anatomic factors
- Requires surgical input and Heart Team
- Unless negative anatomic factors, TAVR preferred

High

High

High

High
**All-Cause Mortality (ITT)**

**All Patients**

- **TAVR**
  - No. at Risk: 348
  - Months post Randomization:
    - 0: 348
    - 12: 262
    - 24: 228
    - 36: 191
    - 48: 154
    - 60: 61

- **SAVR**
  - No. at Risk: 351
  - Months post Randomization:
    - 0: 351
    - 12: 236
    - 24: 210
    - 36: 174
    - 48: 131
    - 60: 64

Error Bars Represent 95% Confidence Limits

HR [95% CI] = 1.04 [0.86, 1.24]

p (log rank) = 0.76
Aortic Valve Mean Gradient

No structural valve deterioration that required re-intervention.

Error bars = ± 1 Std Dev

p < 0.0001
All-Cause Mortality

No. at risk:
- TAVR: 391
- SAVR: 359

[95% confidence intervals]
Valve Hemodynamics

P < 0.01 for TAVR vs. SAVR at all follow-up time points

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1 Year</th>
<th>2 Years</th>
<th>3 Years</th>
<th>4 Years</th>
<th>5 Years</th>
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<tbody>
<tr>
<td>TAVR AVG</td>
<td>391</td>
<td>303</td>
<td>250</td>
<td>193</td>
<td>152</td>
<td>112</td>
</tr>
<tr>
<td>SAVR AVG</td>
<td>359</td>
<td>230</td>
<td>188</td>
<td>141</td>
<td>114</td>
<td>88</td>
</tr>
<tr>
<td>TAVR EOA</td>
<td>384</td>
<td>284</td>
<td>238</td>
<td>182</td>
<td>144</td>
<td>99</td>
</tr>
<tr>
<td>SAVR EOA</td>
<td>353</td>
<td>210</td>
<td>174</td>
<td>134</td>
<td>106</td>
<td>84</td>
</tr>
</tbody>
</table>
TAVR Risk Assessment

TAVR Lower-Risk Strata

Moderate risk = Intermediate risk

- STS ≈ 3 – 8%
- Mean age ≈ 80 yo
- Clearly surgical candidates
- *Choice of TAVR vs. surgery based on clinical/anatomic factors and patient preference*
Primary Endpoint (ITT)
All-Cause Mortality or Disabling Stroke

HR [95% CI] = 0.89 [0.73, 1.09]
p (log rank) = 0.253

Number at risk:
Surgery 1021 838 812 783 770 747 735 717 695
TAVR 1011 918 901 870 842 825 811 801 774
TF Primary Endpoint (ITT)
All-cause Mortality or Disabling Stroke

HR: 0.79 [95% CI: 0.62, 1.00]
p (log rank) = 0.05

Number at risk:
- TF Surgery: 775, 643, 628, 604, 595, 577, 569, 557, 538
- TF TAVR: 775, 718, 709, 685, 663, 652, 644, 634, 612

TF Primary Endpoint (ITT)
All-cause Mortality or Disabling Stroke

Months from Procedure

All-Cause Mortality or Disabling Stroke (%)

- TF Surgery: 4.9%, 7.7%, 12.3%, 15.9%, 20.4%
- TF TAVR: 16.8%
P2A and S3i Perspectives

Key findings

Surgery better

- Vascular complications
- PVR

TAVR better

- Mortality
- Strokes
- AKI
- Severe bleeding
- New onset AF
- Valve area
- 30-day QOL
- 30-day 6MWT
- ICU/hospital LOS
- Days alive OOH

Which therapy do you think is better?
### SURTAVI Trial

#### All-Cause Mortality or Disabling Stroke

<table>
<thead>
<tr>
<th>Months Post-Procedure</th>
<th>No. at Risk SAVR</th>
<th>No. at Risk TAVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>796</td>
<td>864</td>
</tr>
<tr>
<td>18</td>
<td>674</td>
<td>755</td>
</tr>
<tr>
<td>12</td>
<td>555</td>
<td>612</td>
</tr>
<tr>
<td>6</td>
<td>407</td>
<td>456</td>
</tr>
<tr>
<td>24</td>
<td>241</td>
<td>272</td>
</tr>
</tbody>
</table>

#### 24 Months

<table>
<thead>
<tr>
<th></th>
<th>TAVR</th>
<th>SAVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-Cause Mortality or Disabling Stroke</td>
<td>12.6%</td>
<td>14.0%</td>
</tr>
</tbody>
</table>
Disabling Stroke

**SURTAVI Trial**

### Disabling Stroke

![Graph showing disabling stroke rates over time for SAVR and TAVR procedures.]

**No. at Risk**

<table>
<thead>
<tr>
<th>Months Post-Procedure</th>
<th>SAVR</th>
<th>TAVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
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<tr>
<td>0</td>
<td>241</td>
<td>272</td>
</tr>
</tbody>
</table>

**24 Months**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>No. at Risk</th>
<th>95% CI for Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAVR</td>
<td>796</td>
<td>2.6% - 4.0, 0.1</td>
</tr>
<tr>
<td>SAVR</td>
<td>864</td>
<td>4.5%</td>
</tr>
</tbody>
</table>

**95% CI** for difference between TAVR and SAVR is approximately **2.6%** to **4.0%** with a **95% CI of 0.1**.
Severe AS
Symptomatic

Surgical Risk Strata

Low
SAVR
IB

Intermediate
SAVR or TAVR
Iia B

High
SAVR or TAVR
IA

Prohibitive
TAVR
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

IB

IB

IB

Columbia University Medical Center

NewYork-Presbyterian
STS database 2002-2010 (141,905 pts)

The ‘holy grail’ 80% low-risk AS patients!

Courtesy of N. Piazza, V. Thourani
TAVR Risk Assessment

**TAVR Lower-Risk Strata**

**Low risk**

- STS < 3%
- Mean age ≈ 65-80 yo
- Usual surgical patient!
- Subset of bicuspid AV
- Limited clinical data, BUT 4 major RCTS ongoing – data in 2019!
- Will certainly involve a “shared” decision-making process
## NOTION: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic, % or mean ± SD</th>
<th>TAVR n=145</th>
<th>SAVR n=135</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>79.2 ± 4.9</td>
<td>79.0 ± 4.7</td>
<td>0.71</td>
</tr>
<tr>
<td>Male</td>
<td>53.8</td>
<td>52.6</td>
<td>0.84</td>
</tr>
<tr>
<td>Society of Thoracic Surgeons (STS) Score</td>
<td>2.9 ± 1.6</td>
<td>3.1 ± 1.7</td>
<td>0.30</td>
</tr>
<tr>
<td>STS Score &lt; 4%</td>
<td>83.4</td>
<td>80.0</td>
<td>0.46</td>
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<tr>
<td>Logistic EuroSCORE I</td>
<td>8.4 ± 4.0</td>
<td>8.9 ± 5.5</td>
<td>0.38</td>
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<tr>
<td>NYHA class III or IV</td>
<td>48.6</td>
<td>45.5</td>
<td>0.61</td>
</tr>
</tbody>
</table>
NOTION: Death (all-cause), Stroke or MI at 5 Years (as-treated)

CoreValve vs. Surgery in Low-Risk Patients (N = 280)

PIs: H. Gustav Hørsted Thyregod and Lars Sondergaard,
**NOTION:** Valve Performance (echo) thru 5 years (as treated)

*CoreValve vs. Surgery in Low-Risk Patients (N = 280)*

Pis: H. Gustav Hørsted Thyregod and Lars Sondergaard,
The PARTNER 3 Trial
Study Design

Symptomatic Severe Calcific Aortic Stenosis

Low Risk ASSESSMENT by Heart Team (STS < 4%, TF only)

1:1 Randomization (n=1,228)
TF - TAVR (SAPIEN 3) Surgery (Bioprosthetic Valve)

Follow-up: 30 days, 6 mos, 1 year and annually through 10 years

CT Imaging Sub-Study (n=200)

Low Risk ASSESSMENT by Heart Team (STS < 4%, TF only)

PRIMARY ENDPOINT:
Composite of all-cause mortality, all strokes, or re-hospitalization at 1 year post-procedure

Bicuspid Valves (n=50)
SAVR or TAVR ViV (n=100/25)
Mitral ViV or ViR (n=50/50)

PARTNER 3 Registries

Alternative Access (n=100)
(TA/TAo/Subclavian)

Actigraphy/QoL Sub-Study
CT Imaging Sub-Study (n=200)

Follow-up: 30 days, 6 mos, 1 year and annually through 10 years

ACC 2019
MEDTRONIC TAVR RCT IN LOW RISK PATIENTS

TRIAL DESIGN & LEAFLET SUB-STUDY

- **Patient Population: Low Risk Cohort**
  - Determined by Heart Team to be low surgical risk

- **Primary Endpoint:**
  - Safety: Death, all stroke, life-threatening bleeding, major vascular complications, or AKI at 30 days
  - Efficacy: Death or major stroke at 2 years

- **Sample Size:** ~1200 subjects

- **Follow-up Evaluations:**
  - 30-days, 6-month, 18-month, and 1 thru 5 years

- **Number of Sites:** Up to 80 sites

ACC 2019
Who does poorly with TAVR? surgery?
Along the TAVR journey, we studied important TAVR subgroups and aspects of bioprosthetic valve function, patient responses to therapy, and socio-economic impact.
TAVR for Bioprosthetic Valve Failure

Valve-in-Valve

- 365-day and 1-year all-cause mortality was 2.7% and 12.4% respectively.
- 30-day mortality was 3.1%.

Cohort Derivation and Characteristics

Population characteristics
- Mean age 84.5 yrs
- 48% female
- 95% NYHA class 3-4
- 92% obstructive CAD
- Severe AS: AVA 0.65 cm²
- THV size: 52% 23; 48% 26
- Access: 43% TA ; 57% TF

Survival w/o reintervention
- 39% at 5 years by non-adjusted parametric estimate
AV Mean Gradient Population Trends: Early Post Implant and Midterm to 5 Yrs

Raw data

Population trends

Decomposition of trends over time

Early change: 
12.1 to 9.2 mmHg

Late change: 
9.2 to 10.3 mmHg 
Slope: 0.0018± 0.0039
AV Reintervention: Incidence and Case Reviews

- 20 pts with reintervention (9 SAVR, 8 late valve-in-valve, 3 BAV)
- Indication: Structural cause in 5 (25%)
  - AS: n=1; Valve thrombosis: n=1; Trans AR: n=3

Adverse Changes
(N = 4, 20%)
- Classic ↑ gradient, ↓ EOA, ↓ DVI

No Data
(N = 5, 25%)
- No post-implant trial echo data

Adverse Initial
(N = 1, 5%)
- High initial gradient, no change

No Changes
(N = 10, 50%)
- No appreciable or consistent hemodynamic changes
- Last echo data > 1 mo prior to reintervention in 9/10 pts
Valve Safety: Case Reviews of Hemodynamic ‘Outliers’

- **VARC-2 ID’d ‘mild AS’ in 3-48%**
  - Similar rates in SAVR and TAVR
  - Impractical for case review

- **↑ AV mean gradient ≥ 20 mmHg**
  - N=10 (0.45%)
  - 6 deaths (3 CV), no reintervention

- **Any mean gradient ≥ 40 mmHg**
  - N=11 (0.46%)
  - 8 deaths (2 CV), 1 reintervention

- **Any DVI ≤ 0.25**
  - N=44 (1.8%)
  - 22 deaths (5 CV), no reintervention
New EU guidance with standardized definitions and endpoints to assess bioprosthetic aortic valve deterioration and failure

Capodanno D et al. Europ Heart J 2017
Head-to-Head Durability of TAVI vs SAVR

6-Year Outcomes of the NOTION Trial

NOTION: 280 patients at low surgical risk randomized to TAVI or SAVR | Structural Valve Deterioration

<table>
<thead>
<tr>
<th></th>
<th>TAVI</th>
<th>SAVR</th>
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</thead>
<tbody>
<tr>
<td>Structural valve deterioration</td>
<td>3.6%</td>
<td>23.7%</td>
</tr>
<tr>
<td>Moderate haemodynamic SVD</td>
<td>0.7%</td>
<td>3.0%</td>
</tr>
</tbody>
</table>

NOTION: 280 patients at low surgical risk randomized to TAVI or SAVR | Bioprosthetic Valve Failure

<table>
<thead>
<tr>
<th></th>
<th>TAVI</th>
<th>SAVR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valve-related deaths</td>
<td>5.0%</td>
<td>3.7%</td>
<td>0.59</td>
</tr>
<tr>
<td>Re-intervention</td>
<td>2.2%</td>
<td>0.7%</td>
<td>0.62</td>
</tr>
<tr>
<td>Severe haemodynamic SVD</td>
<td>0.7%</td>
<td>3.0%</td>
<td>0.21</td>
</tr>
</tbody>
</table>

ESC Congress Munich 2018

Courtesy: D. Capodanno and L. Sondergaard
Primary Endpoint (PIA RCT)
KCCQ Overall Summary

MCID = 5 points

Growth curve analysis; adjusted for baseline
MCID = minimum clinically important difference

25 point improvement in KCCQ scores
Total 1-Year Costs

\[ \Delta = -15,511 \ (p<0.001) \]

S3-TAVR

- $26,861
- $54,117

SAVR

- $38,238
- $58,250

Follow-up

Index
Hospitalization

* Trimmed means
S3-TAVR vs. SAVR: Cost-Effectiveness

$\Delta$ Long-term Cost (TAVR-SAVR)

$\Delta$ QALYs (TAVR-SAVR)

$\Delta$ Cost = -$9,692$

$\Delta$ QALE = 0.27 yrs

$P(\text{dominant}) = 97%$

$P(\text{ICER}<50K/QALY) = 100%$

* Costs and benefits discounted at 3%
TAVR has become a “routine” procedure in > 1,000 centers worldwide (and almost 600 in the U.S.) for patients with severe symptomatic AS with ≥ moderate surgical risk profiles and appropriate anatomy.

- Trans-femoral is the default approach and minimalist strategies are favored.
- The heart valve team is the central vehicle for coordinating all Dx and Rx decisions.
Current ‘primary’ TAVR technology has stabilized but there are new TAVR systems which are being evaluated in the U.S. and elsewhere.
Current “Standards” for TAVR

MDT Evolut R (PRO)  Edwards Sapien 3
“Next in Line” for TAVR

LOTUS (Edge)    ACURATE neo    PORTICO
“Rebooting” and Increasing Momentum

JENA Valve       CENTERA       VENUS A Valve
TAVR Landscape - 2018

Where are we NOW?

- Current ‘primary’ TAVR technology has stabilized but there are new TAVR systems which are being evaluated in the U.S. and elsewhere.
- New ‘accessory’ TAVR technology may improve procedural outcomes – most recent, has been the introduction of cerebral embolic protection devices.
Clinical studies...

Gennaro Giustino et al

Cerebral Embolic Protection During TAVR
A Clinical Event Meta-Analysis

Compared With Unprotected Procedures

Julia Seeger, MD; Bingid Gonska, MD; Markus Otto, MD; Wolfgang Rottbauer, MD; Jochen Wöhrle, MD
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 Accessory Devices
Cerebral Embolic Protection (CEP)
SENTINEL CEP Randomized Trial

**Embolic Debris Analysis**

**SENTINEL Histopathology:**
Total Embolic Material by Type

- Patients with Captured Material
- ANY: 99%
- Acute Thrombus & Tissue/Foreign Material: 98%
- Arterial Wall: 94%
- Valve Tissue: 50%
- Calcification: 50%

**Patient Quartile Analysis:**
Average Number of Particles $\geq 0.5$ mm

- 1 in 4 Patients had 25 Particles $\geq 0.5$ mm in Size

**Average # of Particles Captured $\geq 0.5$ mm**
- Q1: 0.9
- Q2: 3.7
- Q3: 8.9
- Q4: 25.1

*Automated measurement*
SENTINEL CEP Randomized Trial

Clinical Outcomes

Stroke Diagnosis ≤72 hours (ITT)

<table>
<thead>
<tr>
<th>Days to Stroke</th>
<th>Sentinel</th>
<th>Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>1.3%</td>
<td>4.5%</td>
<td></td>
</tr>
<tr>
<td>Day 2</td>
<td>0.4%</td>
<td>0.9%</td>
<td></td>
</tr>
<tr>
<td>Day 3</td>
<td>1.3%</td>
<td>2.7%</td>
<td>0.052*</td>
</tr>
<tr>
<td>Total</td>
<td>3.0%</td>
<td>8.2%</td>
<td>63% Reduction</td>
</tr>
</tbody>
</table>

p=0.052* (Fisher Exact Test)
CEP Meta-analysis

Five Studies (n = 625 patients)

- Meta-analysis of 5 RCTS of CEP in TAVR (625 pts; 376 with CEP and 249 without CEP)
- > 40% reduction in risk of stroke or death (6.4% vs 10.8%; RR: 0.57; 95% CI: 0.33-0.98; p=0.04; I² = 0%)
- **NNT = 22 to reduce one stroke or death**

Giustino G et al. JACC 2017
Cerebral Embolic Protection Protection (CEP) 
SENTINEL ULM Experience

- 802 all-comer consecutive TAVR patients at University of Ulm were prospectively enrolled
- A propensity-score analysis was done matching the 280 patients protected with Sentinel to 280 control patients

Cerebral Embolic Protection During Transfemoral Aortic Valve Replacement Significantly Reduces Death and Stroke Compared With Unprotected Procedures

Julia Seeger, MD, Birgid Gonska, MD, Markus Otto, MD, Wolfgang Rottbauer, MD, Jochen Wöhrle, MD

mortality and stroke at 7-days

Wörhle J, Seeger J, et al. DGK Mannheim 2017; CSI-Ulm-TAVR Study clinicaltrials.gov NCT02162069
## Sentinel CEP with TAVR

### ‘Real world’ registries - stroke reduction

<table>
<thead>
<tr>
<th>Study Center</th>
<th>Unprotected TAVR Patients Neuro Event Rate % (n/N)</th>
<th>Sentinel TAVR Patients Neuro Event Rate % (n/N)</th>
<th>Relative Risk Reduction (RRR)</th>
<th>Number-needed-to-treat (NNT) to avoid one event</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ulm University¹</strong></td>
<td>4.6% (13/280)</td>
<td>1.4% (4/280)</td>
<td>70%</td>
<td>22</td>
</tr>
<tr>
<td>• N=560</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• May 2017</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pinnacle Health²</strong></td>
<td>10% (7/69)</td>
<td>0% (0/53)</td>
<td>100%</td>
<td>10</td>
</tr>
<tr>
<td>• N=122</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Feb 2018</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Erasmus and University Med Centers in Rotterdam</strong></td>
<td>5.4% (32/589)</td>
<td>1.4% (7/485)</td>
<td>74%</td>
<td>25</td>
</tr>
<tr>
<td>and Groningen³</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• N=1047</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• June 2018</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cedars Sinai⁴</strong></td>
<td>3.6% (21/589)</td>
<td>0.8% (4/485)</td>
<td>78%</td>
<td>36</td>
</tr>
<tr>
<td>• N=440</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• June 2018</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹ Ulm University: N=560, May 2017
² Pinnacle Health: N=122, Feb 2018
³ Erasmus and University Med Centers in Rotterdam and Groningen: N=1047, June 2018
⁴ Cedars Sinai: N=440, June 2018
Cerebral Embolic Protection (CEP)

Is it necessary?

Would you take a chance and drive without a seatbelt?

You never know when you’ll need protection!
What the future will bring...
TAVR Landscape - 2018

Speculations and Predictions
The success of TAVR therapy has catalyzed a ‘second wave’ of clinical studies to explore the expansion of clinical indications (even beyond current surgery).

- Bicuspid AV disease
- AS + concomitant disease (CAD, MR, AF)
- Severe asymptomomatic AS
- Moderate AS + CHF
- High-risk severe AR
Incidence of BAV in Isolated SAVR

Frequency by Decades of Unicuspid, Bicuspid, and Tricuspid Aortic Valves in Adults Having Isolated Aortic Valve Replacement for Aortic Stenosis, With or Without Associated Aortic Regurgitation

William C. Roberts, MD; Jong M. Ko, BA

932 SAVR patients

- Bicuspid (49%)
- Tricuspid (45%)
- Others (6%)

Age (Year)
BAV Classification

CTA System

(from 14 centers in North America, Europe and Asia)

**Tricommissural**
- 3 commissures
- V-like orifice
- “functional or acquired”

**Bicommissural**
- Raphe-type
  - 2 commissures, 1 raphe
  - Slit-like orifice

- Non Raphe-type
  - 2 commissures, no raphe
  - Slit-like orifice
Recent Multicenter BAV – TAVI Registry

Yoon SH et al. JACC 2017;21:2579-89
Bicuspid vs. Tricuspid TAVR Outcomes
A Propensity-Matched Analysis from the TVT Registry

63581 SAPIEN 3 Cases in TVT Registry
(June 2015 – Feb 2018)

1:1 Propensity Matching

- 1:1 subject selection
- 24 baseline covariates
- Missing values: imputed using Markov Chain Monte Carlo method
- Logistic regression model

5161 N/A, Uncertain, Unicuspid, Quadricuspid
1605 Valve-in-Valve

55023 Tricuspid AS SAPIEN 3 Patients

1792 Bicuspid AS SAPIEN 3 Patients
386 Sites

1792 Bicuspid AS SAPIEN 3 Patients
1:1 Propensity Matching

1792 Tricuspid AS SAPIEN 3 Patients
424 Sites

Raj Makkar; TCT 2018
Bicuspid vs. Tricuspid TAVR Outcomes
A Propensity-Matched Analysis from the TVT Registry

Raj Makkar; TCT 2018

1-Year All-Cause Mortality

HR: 1.10 [95% CI: 0.83, 1.47]
Log rank P= 0.506

Number at risk:
Bicuspid 1792
Tricuspid 1792

0 5 10 15 20 25 30 35 40
Mortality (%)

0 3 6 9 12
Time in Months

Bicuspid Tricuspid

10.4% 10.8%
Bicuspid vs. Tricuspid TAVR Outcomes
A Propensity-Matched Analysis from the TVT Registry

1-Year All Strokes

HR: 1.87 [95% CI: 1.17, 2.99]
Log rank P = 0.008

Number at risk:

<table>
<thead>
<tr>
<th></th>
<th>Bicuspid</th>
<th>Tricuspid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time in Months</td>
<td>1 Year</td>
<td>3.4%</td>
</tr>
<tr>
<td></td>
<td>2 Years</td>
<td>2.7%</td>
</tr>
</tbody>
</table>

Raj Makkar; TCT 2018
Bicuspid vs. Tricuspid TAVR Outcomes
A Propensity-Matched Analysis from the TVT Registry

Para-Valvular Leak

<table>
<thead>
<tr>
<th></th>
<th>Bicuspid (n=1422)</th>
<th>Tricuspid (n=1466)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharge</td>
<td>0.1%</td>
<td>0.0%</td>
<td>0.26</td>
</tr>
<tr>
<td></td>
<td>17.7%</td>
<td>16.6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>80.7%</td>
<td>82.4%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Bicuspid (n=1105)</th>
<th>Tricuspid (n=1153)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day</td>
<td>0.1%</td>
<td>0.3%</td>
<td>0.71</td>
</tr>
<tr>
<td></td>
<td>25.2%</td>
<td>24.2%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>72.1%</td>
<td>73.2%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Bicuspid (n=306)</th>
<th>Tricuspid (n=362)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-year</td>
<td>0.3%</td>
<td>0.0%</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>25.2%</td>
<td>24.0%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>69.9%</td>
<td>73.2%</td>
<td></td>
</tr>
</tbody>
</table>
Aortic Stenosis & Atrial Fibrillation

**Watch-TAVR**

1° Outcome:
- Death, stroke, bleeding @ 1 year

2° Outcome:
- Components of primary
- Any thromboembolism
- Cardiovascular death
- Re-hospitalization
- QoL (KCCQ-12)
- Procedural costs

**TAVR + WATCHMAN**
(n = 156)

**TAVR + Medical Rx**
(n = 156)

National PIs: Samir Kapadia & Martin Leon
Grant support: Boston Scientific
Early TAVR Trial
Study Flow

Asymptomatic Severe AS and 2D-TTE (PV ≥4m/s or AVA ≤1 cm²)
Exclusion if patient is symptomatic, age <65 yo, EF<50%, concomitant surgical indications, or STS >8

Treadmill Stress-Test

- Stress-Test Normal
  - CTA and Angiography
  - TF- TAVR eligibility

- Early-TAVR Randomized Trial
  - Randomization 1:1
    - Stratified by STS (<3 vs ≥3)
  - TF- TAVR
  - Clinical Surveillance

- Stress-Test Abnormal
  - Early TAVR Registry

Primary Endpoint (superiority): 2-year composite of all-cause mortality, all strokes, and repeat hospitalizations (CV)

1109 pts, 75 US sites

Principal Investigators:
Philippe Généreux, Allan Schwartz
Chair: Martin B. Leon
TAVR UNLOAD Trial

Study Design

(600 patients, 1:1 Randomized)

PIs: Nicolas M. Van Mieghem and Martin B. Leon

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

Follow-up:
- 1 month
- 6 months
- 1 year

Clinical endpoints
Symptoms
Echo
QoL

TAVR UNLOAD Trial
International Multicenter Randomized

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

TAVR + OHFT

OHFT Alone

Reduced AFTERLOAD
Improved LV systolic and diastolic function
Jena Valve TAVR System

Ongoing EFS for AS and AR

Features

- self-expanding nitinol frame
- bovine pericardial leaflets
- supra-annular valve position
- clipping of native leaflets
- mitigated risk of coronary obstruction, new PPM, and annulus rupture due to pre-defined position in the annulus

Valve sizes: 23, 25, and 27 mm
The success of TAVR therapy has catalyzed a ‘second wave’ of clinical studies to explore the expansion of clinical indications (even beyond current surgery).

There are many innovative TAVR-related technologies which are being actively explored!
Tissue Engineered Heart Valves

the promise...

Non living

Mechanical valves

Bioprosthetic valves

Living

1960

One valve for life!

2020
Zurich Tissue Engineered Heart Valve

A “Living” Aortic Valve

Courtesy of Simon P. Hoerstrup, MD, PhD
Endogenous tissue restoration

*combining 3 scientific disciplines*

Jean Marie Lehn
Nobel prize for Supramolecular Chemistry, 1987

Sijbesma, Science, 1997
Xeltis

Endogenous Tissue Restoration (ETR)

• Synthetic matrix made of novel bioabsorbable 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)*

- Safety demonstrated in >50 sheep
- 96% device success
- 3 and 6 months FU complete
- Preliminary 12 months data available and encouraging
- Hemodynamic performance stable over time

**Aortic Valve**
Novel AS Imaging Technology

Bay Labs – Echo acquisition

Available hand-held POCUS devices

Prompts for BL echo acquisition

JAMA Cardiology 2018

POCUS = point-of-care ultrasound
Novel AS Imaging Technology

Bay Labs – Echo interpretation

Training: > 25,000 complete AS echo studies

Input: PLAX and PSAX shown to the pre-trained network

Output: network integrates responses and makes diagnosis of valvular heart disease, rheumatic vs. non-rheumatic, and estimates the severity of AS (when present)
TAVR Accessory Devices

Aortic Valve Remodeling (1)

Leaflex AVRT

- Mechanical scoring blades fracture leaflet calcium and improve leaflet mobility
- 13 Fr catheter
- Non-occlusive (no PM)
- Can be used as (1) stand-alone, (2) bridge to TAVR/SAVR or (3) preparation for TAVR (heavily calcified valves)
TAVR Accessory Devices

Aortic Valve Remodeling (2)

Lithoplasty for Aortic Leaflet Restoration

- *Electro-hydraulic lithotripsy in a balloon*; microsecond bubble expansion and collapse travels thru balloon and disrupts calcium
- Supra-vavular approach
- Procedural hemodynamic stability; no need for PM
- Trans-femoral access
- Preparation for TAVR preparation or stand-alone therapy
The success of TAVR therapy has catalyzed a ‘second wave’ of clinical studies to explore the expansion of clinical indications (even beyond current surgery).

There are many innovative TAVR-related technologies which are being actively explored!

In the future, AS classification schemes and therapy trigger points will be redefined.
Staging classification of aortic stenosis based on the extent of cardiac damage

Philippe Généreux¹,²,³, Philippe Pibarat⁴, Björn Redfors¹,⁵, Michael J. Mack⁶, Raj R. Makkar⁷, Wael A. Jaber⁸, Lars G. Svensson⁸, Samir Kapadia⁸, E. Murat Tuzcu⁸, Vinod H. Thourani⁹, Vasilis Babaliaros⁹, Howard C. Herrmann¹⁰, Wilson Y. Szeto¹⁰, David J. Cohen¹¹, Brian R. Lindman¹², Thomas McAndrew¹, Maria C. Alu¹³,

<table>
<thead>
<tr>
<th>Stage/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>No Cardiac Damage</td>
<td>LV Damage</td>
<td>LA or Mitral Damage</td>
<td>Pulmonary Vasculature or Tricuspid Damage</td>
<td>RY Damage</td>
<td></td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>Increased LV Mass Index &gt;115 g/m² (Male) &gt;95 g/m² (Female)</td>
<td>Indexed left atrial volume &gt;34mL/m²</td>
<td>Systolic Pulmonary hypertension ≥60 mmHg</td>
<td>Moderate-Severe right ventricular dysfunction</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>Atrial Fibrillation</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Staging classification of aortic stenosis based on the extent of cardiac damage

Number at risk:

Time in Months

Death (%)
New Hypothesis: Ventricular, Valvular and Vascular Dynamics Drive Aortic Stenosis (and should influence treatment decisions)

Courtesy of E. Edelman and colleagues
There are also many ‘gaps’ in TAVR knowledge which must be addressed (e.g. valve leaflet abnormalities, late TAVR SVD/durability, coronary access considerations, and optimal adjunctive pharmacotherapy).
Severely reduced leaflet motion noted in 2 patients in the early part of the U.S. Portico IDE study.
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*
Coronary Angiography and Percutaneous Coronary Intervention After Transcatheter Aortic Valve Replacement

Matias B. Yudi, MBBS, Samin K. Sharma, MD, Gilbert H.L. Tang, MD, MSc, MBA, Annapoorna Kini, MD

CENTRAL ILLUSTRATION  Coronary Reaccess After TAVR

Factors Impacting Coronary Access

- **Anatomical**
  1. Sinotubular junction dimensions
  2. Sinus height
  3. Leaflet length and bulkiness
  4. Sinus of Valsalva width
  5. Coronary height

- **Device and Procedural**
  1. Commissural tab orientation
  2. Sealing skirt height
  3. Valve implant depth

Fluoroscopy

MDCT

TAVR Adjunct Pharmacology

**Customized Patient-Based Therapy**

**BEFORE**
- Acetylsalicylic acid (ASA)

**DURING**
- **UNFRACTIONATED HEPARIN:**
  - target ACT ≥300
- **Bivalirudin:**
  - **BRAVO**
  - Low Molecular Weight Heparin

**AFTER**
- **ASA + CLOPIDOGREL**
- **Acetylsalicylic acid (ASA)**
- **ARTE trial**
- **Non anti-VKA Oral Anticoagulant ± ASA:**
  - **GALILEO**
There are also many ‘gaps’ in TAVR knowledge which must be addressed (e.g. valve leaflet abnormalities, late TAVR SVD/durability, coronary access considerations, and optimal adjunctive pharmacotherapy).

By all meaningful criteria, TAVR has been a BREAKTHROUGH Technology!
Aortic Stenosis

By JOHN ROSS, JR., M.D. AND EUGENE BRAUNWALD, M.D.

The advent of corrective operations for various forms of heart disease has placed increasing emphasis upon the need for accurate information concerning the natural history of patients with potentially correctible lesions. An understanding of the natural course assumes particular importance in the case of aortic stenosis because of the significant incidence of sudden death associated with this disease and the grave prognosis that appears to accompany the onset of certain symptoms,

patients with isolated valvular aortic stenosis of rheumatic etiology and patients without a history of rheumatic fever who have isolated calcific aortic stenosis; many of the latter patients are now considered to have developed calcification and stenosis of a congenitally bicuspid valve. The review will focus primarily...
The Patients are Simply AMAZING!

Patient #1

92 yo man with critical AS…
TAVI at CUMC on 2/8/06…
Playing golf in Palm Springs on 3/8/06!!!
It’s is All About the Patients!

Remember, your patients are the point-of-care!!!