Transcatheter Aortic Valve Replacement: Where am I now, and where are we going?

Dustin Kliner, MD – Clinical Assistant Professor of Medicine
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Disclosures

- Coinvestigator in trials involving Edwards Sapien, Medtronic Evolut, Boston Scientific Lotus and St. Jude Portico
- No financial disclosures

- Most importantly, I believe more in quality of life than quantity of life

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Objectives

• Discuss (briefly) the obligatory etiology, epidemiology, and pathophysiology of aortic stenosis as it relates to TAVR
• Review the current indications and guidelines for use of TAVR
• Highlight the most recent large scale TAVR trials using current generation valves
• Preview some upcoming directions of TAVR
Aortic Stenosis - Etiology

- <70 years old
  - Bicuspid – 50%
  - Postinflammatory (rheumatic) - 25%
  - Degenerative – 18%
  - Unicuspid, hypoplastic, undetermined, etc – 7%
- > 70 years old
  - Degenerative – 48%
  - Bicuspid – 27%
  - Postinflammatory (rheumatic) – 23%
Degenerative AS

Severe Aortic Stenosis is often caused by calcification of the aortic valve’s leaflets

Images courtesy of Renu Virmani MD at the CVPath Institute

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Aortic Stenosis - Diagnosis

- H&P – CHF, characteristic murmur
- TTE

Table 1. Criteria for aortic stenosis in patients with normal left ventricular function

<table>
<thead>
<tr>
<th>Severity</th>
<th>Valve Area (cm²)</th>
<th>Mean Gradient (mmHg)</th>
<th>Velocity (m/s)</th>
<th>Indexed Valve Area (cm²/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>&gt;1.5</td>
<td>&lt;20</td>
<td>2.6-2.9</td>
<td>&gt;0.85</td>
</tr>
<tr>
<td>Moderate</td>
<td>1.0-1.5</td>
<td>20-40</td>
<td>3.0-4.0</td>
<td>0.60-0.85</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;1.0</td>
<td>&gt;40</td>
<td>&gt;4.0</td>
<td>&lt;0.6</td>
</tr>
<tr>
<td>Critical</td>
<td>&lt;0.5</td>
<td>--</td>
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</tbody>
</table>
Aortic Stenosis - Symptoms

- Especially in TAVR patients, difficult to elicit, and can be nonexistent
  - CHF – try to assess NYHA class
    - Ask family members – Can they still keep up?
    - If they don’t have CHF, why are they on Lasix?
  - Syncope/Presyncope
  - Angina – Late, ? CAD
- Fatigue?
Abnormal Aortic Valve With Reduced Systolic Opening

Severe AS
- $V_{max} \geq 4$ m/s
- $\Delta P_{mean} \geq 40$ mm Hg

- Symptomatic (stage D1)
  - LVEF <50%
    - (stage C2)
      - Other cardiac surgery
    - $V_{max} \geq 5$ m/s
      - $\Delta P_{mean} \geq 60$ mm Hg
      - Low surgical risk
    - Abnormal ETT
      - $\Delta V_{max} > 0.3$ m/s/y
      - Low surgical risk

- Asymptomatic (stage C)
  - $V_{max} 3$ m/s–3.9 m/s
    - $\Delta P_{mean} 20–39$ mm Hg
      - Symptomatic
        - LVEF <50%
          - YES
            - DSE with
              - $AVA \leq 1$ cm$^2$
              - $V_{max} \geq 4$ m/s
                - (stage D2)
              - AS likely cause of symptoms
          - NO
            - $AVA \leq 1$ cm$^2$
              - LVEF $\geq 50$
                - (stage D3*)
                  - Low surgical risk

- Asymptomatic (stage B)
  - Other cardiac surgery

AVR (I)
AVR (IIa)
AVR (IIb)
AVR (IIa)
Aortic Stenosis in the Elderly

- Retrospective cohort study of 277 patients from a large university database with Doppler derived AVA of \( \leq 0.8 \text{cm}^2 \) and age >80
  - Age 85 \( \pm 4 \) years, 53% male, AV area 0.68 \( \pm 0.16 \text{ cm}^2 \), EF 52 \( \pm 20\% \), CAD 47\%, diabetes 17\%
  - Mean follow up of 2.5 years, during which 55 (20\%) had AVR and 175 deaths occurred
  - In patients with AVR – 1-year, 2-year and 5-year survival rates were 87, 78 and 68\% respectively
  - In patients without AVR - 52, 40 and 22\%, respectively ( \( p < 0.0001 \) )

Aortic Stenosis in the Elderly

- “Conclusion: Prognosis of medically managed severe calcific AS in the elderly patients is dismal. AVR appears to improve survival of these patients and should be strongly considered in the absence of other major comorbidities”
Dr. Alain Cribier
History of TAVR

- Initially based on the observation that low pressure balloon inflation during BAV opened the AV in a circular fashion, restenosis occurred soon after
- Started with stent placement in the AV in animals, and autopsy studies showing expansion
- A small startup in New Jersey began working on a transcatheter valve
- First human implant on April 16, 2002 in France
  - 57 year old, EF 12%, inoperable, presenting with cardiogenic shock
  - Survived the operation, died of multisystem organ failure pre-discharge

- In 2004 the small startup was acquired by Edwards Lifesciences
Who can we treat with TAVR?

- Inclusion criteria for the original TAVR trials were AVA ≤1.0cm² AND peak AV velocity ≥4m/s or mean gradient ≥40mmHg with normal LVEF
- With low EF, augmentation to mean gradient ≥40mmHg or peak AV ≥4m/s with persistent AVA ≤1.0cm² was required
- Bicuspid AV disease, severe LV dysfunction (EF <20%), ESRD on Hemodialysis, or severe regurgitant disease of another valve were exclusion criteria
- Commercial indications are less stringent, but data showing benefit are from smaller trials, or extrapolated, for prior exclusions
Who can we treat with TAVR?

• Society for Thoracic Surgeons (STS) score is calculated on every patient referred for consideration
• Done online or with smart phone app
• Incremental risks for objective frailty, lung disease, liver disease, diastolic dysfunction, etc. are added
• Risks must be adjudicated by two cardiac surgeons who perform independent evaluation and agree with the risk assessment
• Estimated the risk of death on the table, or within 30 days of a cardiac surgery
Commercial Indications

- Extreme surgical risk – TAVR the only option (Class I)*
  - STS score >15% for mortality
- High surgical risk – TAVR preferred (Class I)
  - STS score 8-15% for mortality
- Intermediate risk – TAVR FDA approved (Class IIa)
  - STS score 3-8% for mortality
- Low Risk – Surgical AVR (Class I)
  - STS score <3% for mortality
Is my patient going to benefit from TAVR?
### Choice of Intervention – A Moving Target

#### 2014 Valvular Heart Disease Guidelines

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical AVR is recommended in patients who meet an indication for AVR (Section 3.4) with low or intermediate surgical risk (Section 2.5 in the full-text guideline)</td>
<td>I</td>
<td>A (69,70)</td>
</tr>
<tr>
<td>For patients in whom TAVR or high-risk surgical AVR is being considered, members of a Heart Valve Team should collaborate to provide optimal patient care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAVR is recommended in patients who meet an indication for AVR for AS who have a prohibitive surgical risk and a predicted post-TAVR survival &gt;12 mo</td>
<td>I</td>
<td>C N/A</td>
</tr>
<tr>
<td>TAVR is a reasonable alternative to surgical AVR in patients who meet an indication for AVR (Section 3.4) and who have high surgical risk (Section 2.5 in the full-text guideline)</td>
<td>Iia</td>
<td>B (73,74)</td>
</tr>
<tr>
<td>Percutaneous aortic balloon dilation may be considered as a bridge to surgical or transcatheter AVR in severely symptomatic patients with severe AS</td>
<td>Iib</td>
<td>B (73,74)</td>
</tr>
<tr>
<td>TAVR is not recommended in patients in whom existing comorbidities would preclude the expected benefit from correction of AS</td>
<td>III: No Benefit</td>
<td>B (71)</td>
</tr>
</tbody>
</table>

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Choice of Intervention – A Moving Target

- 2017 Focused Update to Valvular Heart Disease Guidelines

Nishimura et al. 2017 AHA/ACC Focused Update in Valvular Heart Disease

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Intermediate Risk

• TAVR or SAVR may be appropriate, multiple factors considered
  – Age of the patient
  – Presence of absence of CAD and the need for revascularization
  – Availability of iliofemoral access for TAVR
  – Size of aortic annulus or unfavorable annular anatomy secondary to heavy calcification (higher risk for annular injury or paravalvular leak)
  – Patient preference

  – If both are considered acceptable to cardiology and cardiac surgery, risks and benefits of each are discussed and the patient chooses
S3i – Intermediate risk

- 2032 patients, 57 centers, randomized to SAVR or TAVR
- Further split based on access routes into transfemoral or transthoracic
- Rates of death and disabling CVA were similar (19.3% TAVR vs 21.2% SAVR 0.89, [CI] 0.73-1.09, p=0.25
- At 2 years, TAVR in the transfemoral access cohort resulted in a lower rate of death and disabling CVA (HR 0.79, 0.62 to 1.00, p=0.05), with similar outcomes in the transthoracic group
- TAVR resulted in larger aortic valve areas, lower rates of AKI, severe bleeding, and new Afib while surgery resulted in fewer vascular complications and less aortic regurgitation

S3i – Intermediate risk

A Intention-to-Treat Population

Hazard ratio, 0.89 (95% CI, 0.73–1.09)
P = 0.25

Death from Any Cause or Disabling Stroke (%)

Surgery 16.4 14.5 21.1
TAVR 14.5 21.1

0 3 6 9 12 15 18 21 24
No. at Risk
TAVR 1011 918 901 870 842 825 811 801 774
Surgery 1021 838 812 783 770 747 735 717 695

B As-Treated Population

Hazard ratio, 0.87 (95% CI, 0.71–1.07)
P = 0.18

Death from Any Cause or Disabling Stroke (%)

Surgery 16.6 14.0 21.0
TAVR 14.0 18.9

0 3 6 9 12 15 18 21 24
No. at Risk
TAVR 994 917 900 870 842 825 811 801 774
Surgery 944 826 807 779 768 743 731 715 694

C Transfemoral-Access Cohort, Intention-to-Treat Analysis

Hazard ratio, 0.79 (95% CI, 0.62–1.00)
P = 0.05

Death from Any Cause or Disabling Stroke (%)

Surgery 15.9 12.3 20.4
TAVR 12.3 16.8

0 3 6 9 12 15 18 21 24
No. at Risk
TAVR 775 718 709 685 663 652 644 634 612
Surgery 775 643 628 604 595 577 569 557 538

D Transfemoral-Access Cohort, As-Treated Analysis

Hazard ratio, 0.78 (95% CI, 0.61–0.99)
P = 0.04

Death from Any Cause or Disabling Stroke (%)

Surgery 15.8 11.7 20.0
TAVR 11.7 16.3

0 3 6 9 12 15 18 21 24
No. at Risk
TAVR 762 717 708 685 663 652 644 634 612
Surgery 722 636 624 600 591 573 565 555 537
• 1746 patients at 87 centers (we were one) with severe, symptomatic AS and intermediate surgical risk (STS 3-8%)
• Mean age 79.8 ± 6.2 years, mean STS 4.5±1.6%
• At 24 months the composite end point of all cause mortality or disabling CVA was present in 12.6% of the TAVR group and 14.0% in the surgery group (noninferior)
• Surgery had higher rates AKI, transfusion, and Afib
• TAVR had higher rates of residual AI, and need for PPM
• No difference in structural valve deterioration at 24 months.
• “increase in PPM rate” is not trivial, 25.9% vs 6.6% with surgery

What about low risk?

- We are currently enrolling in the Medtronic TAVR in Low Risk Patients Trial
  - Planned 1200 patients
  - Open label 1:1 randomization of Medtronic Evolut TAVR vs SAVR in patients at low risk for SAVR
  - Primary endpoint – all cause mortality or disabling CVA at 2 years
  - Secondary endpoints are multiple
    - Follow up annually for 10 years to assess quality of life and valve degeneration via TTE
What about low risk?

• Inclusion Criteria
  – Symptomatic patients
    • AVA ≤ 1cm² (index ≤ 0.6cm²) OR mean gradient ≥40mmHg OR peak AV velocity ≥4m/s
  – Asymptomatic patients
    • AVA ≤ 1cm² (index ≤ 0.6cm²) AND peak AV velocity ≥5m/s or mean gradient ≥60mmHg
    • Severe AS with symptoms on exercise tolerance test
    • Severe AS with LVEF <50%
  – Documented agreement of heart team that predicted risk of mortality for SAVR is <3% at 30 days
And Valve in Valve…

- Evolut and S3/SXT have an indication for TAVR inside degenerated surgical bioprosthetic valves
  - Can be done for AS or AI – Almost a 50-50 split in studies
  - Must be intermediate or high risk for surgery (STS >3% or incrementals)
  - The type and size of the prior prosthesis must be known
  - 19mm prosthesis are too small for TAV in SAV and not recommended (its been done elsewhere, the mean gradients immediately post op are high 20s)
  - In appropriately sized VIV, the gradients are quite low because of the supraannular valve with Evolut
FDA Approval

- Edwards Sapien – November 2, 2011 – Inoperable – Partner B
- Edwards Sapien – October 19, 2012 – High risk – Partner A
- Medtronic CoreValve – January 2014 - High risk – CoreValve Pivotal
- Edwards Sapien XT – June 16, 2014
- Medtronic CoreValve – March 30, 2015 – Valve in valve TAVR for degenerated bioprosthesis – high risk
- Medtronic Evolut – June 2015
- Edwards Sapien 3 – June 17, 2015
- Edwards Sapien 3 and XT – August 18, 2016 – Intermediate risk - S3i
- Medtronic Evolut Pro – March 22, 2017
How Long Will This Thing Last Anyway?

• Data from Europe out to 9 years*
  – Analysis actually truncated at 7 years, 68.1% of patients had died
  – ~2300 patents studied
  – Twenty prosthesis related clinical events, 14 leading to hospitalization and 6 leading to death
  – Paravalvular leak/regurgitation rates remained similar to those at 1 year follow up
  – NO evidence of early restenosis

  – Keep in mind, this data uses the first 2 generations of the Medtronic Valve, not the generation we’re using today
Evolution of TAVR Valves

• Smaller caliber devices – Less Stroke
  – Edwards Sapien sheaths were 22 and 24Fr, 14 and 16Fr for S3
  – Medtronic Corevalve 18Fr, Evolut R and Pro 14Fr

• Ability to reposition – Less multi-valve deployment
  – Applies to self expanding valves after initial deployment
  – Balloon expandable with fine adjustment available prior to deployment

• Improvement in paravalvular regurgitation
  – Sealing “skirt” material within the annulus
  – Inversely proportional to pacemaker rates
Edwards Sapien Evolution

Edwards Sapien (A), Sapien XT (B), and Sapien 3 (C)
Edwards Sapien Delivery System
Edwards Sapien Evolution

• Paravalvular Leak Reduction
  – Partner B, ≥ moderate PVL in 11.8% at 30 days and 10.5% at 1 year in the extreme risk cohort
  – S3i, ≥ moderate PVL of 1.5% at 1 year

• …At the cost of Pacemaker rate
  – Pacemaker rate higher with S3 > SXT > Sapien
    • 19% vs 12.4% vs 4.5%
Medtronic Corevalve Evolution

17\(^{\dagger}\)/18

- Evolut PRO 23 mm
- Evolut PRO 26 mm
- Evolut PRO 29 mm
- Evolut R 34 mm

30 mm

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Medtronic CoreValve Delivery System

UPMC Heart and Vascular Institute
Medtronic CoreValve Evolution

- Paravalvular Leak Reduction
  - CoreValve pivotal Extreme risk ≥ moderate PVL of 11.4% at 1 month, 4.3% at 1 year
  - Evolut PRO clinical study (n=60) with 0% moderate or severe PVL at 1 month

  - Less change observed in new pacemaker rate than with Sapien, but initial numbers were higher
  - The Evolut PRO clinical study had a rate of 10%, but I suspect the jury is still out
What about asymptomatic patients?

Previously, risk benefit ratios were felt to be favorable only when symptoms had developed or EF had dropped.

Does the availability of a lower risk intervention reset the threshold?
Asymptomatic Patients - EARLY TAVR

• Evaluation of Transcatheter Aortic Valve Replacement Compared to Surveillance for patients with Asymptomatic Aortic Stenosis (EARLY TAVR)
  – Prospective, randomized, 1:1 to TAVR with Edwards Sapien 3 or clinical surveillance
  – Stratified as to whether or not they are able to perform a stress
  – Open to age 65 and older, severe AS, asymptomatic
  – Estimated enrollment 1109, starting this month, primary data collection to complete in December 2020
Conclusions

- TAVR is the preferred option for patients at extreme or high surgical risk, and may be a viable option for those at intermediate risk
- The indications are likely to expand, shifting the paradigm of AS treatment as experience with devices increased
- There is still a role for surgery in young, healthy patients in whom valve longevity is a concern
- Guidelines are largely unable to keep up with the speed of device innovation
Questions?

- Thank you for having me!

- Feel free to contact me with additional questions
- klinerde@upmc.edu