Disclosures

• Clinical Trial Investigator
  - PARTNER 2: Transcatheter aortic valve trial sponsored by EdwardsLifesciences
  - EVEREST/REALISM/COAPT: Transcatheter mitral valve repair trial sponsored by Abbott

• National Steering Committee Clinical Trials
  - RESPECT: PFO closure trial sponsored by St. Jude
  - ACP: LAA occlusion trial sponsored by St. Jude

• Joint Research and Development Projects
  - Philips Medical: Various image guidance studies

Case

• You admit an 85 year old woman with new CHF, syncope, and a loud systolic murmur. She is otherwise functional and healthy except for presumed COPD requiring intermittent home oxygen. Echo shows critical aortic stenosis. CXR shows a calcified ascending aorta. The consulting surgeon says her risk for AVR is excessive. What is a reasonable next step for you?
  1. Arrange home care with hospice or a nursing home.
  2. Get another surgical opinion.
  3. Refer to a Valve Clinic where there is a transcatheter valve team with good outcomes.
  4. Propose aortic balloon valvuloplasty for palliation.
  5. Start standard CHF meds and a statin to slow the progression of her aortic stenosis.
You speak with a clinician at a TAVR program. Which are reasonable next steps in her evaluation?

1. Calculate an STS risk score.
2. Get a combined cardiac and vascular CTA to assess femoral artery access and aortic annular dimensions.
3. Order a cardiac catheterization to determine her coronary status.
4. Perform a treadmill stress test to see if she is too frail for TAVR.
5. Perform PFT’s.

What is Structural Heart Disease?

- A broad family of unrelated cardiac diseases that are either congenital or acquired states characterized by involvement of the cardiac chambers or valves.
- Novel therapies are emerging that are interventional in nature and are transforming care.

<table>
<thead>
<tr>
<th>FDA APPROVED</th>
<th>FDA VERDICTS SOON</th>
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<tbody>
<tr>
<td><strong>ASD</strong></td>
<td><strong>MitraClip for Mitral Regurgitation</strong></td>
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<tr>
<td><strong>VSD</strong></td>
<td><strong>AMPLATZER PFO Occluder after Cryptogenic CVA</strong></td>
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<td><strong>PDA Plugs</strong></td>
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<td>Sapien Sapien Sapien</td>
<td>Watchman for LAA Occlusion in AFib</td>
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<td><strong>TAVR For Aortic Stenosis</strong></td>
<td>CoreValve For Aortic Stenosis</td>
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What Are The Major Developments in SHD You Must Understand?

1. The treatment of aortic stenosis has undergone a fundamental shift with the emergence of TAVR – transcatheter aortic valve replacement.
2. Other valve problems such as mitral regurgitation, bioprosthetic degeneration, congenital pulmonary outflow dysfunction, and paravalvular leak are also undergoing a major evolution.
3. Atrial septal defect closure is now predominantly treated with devices but it is not detected in 50% until adulthood.
4. Stroke risk reduction with LAA occlusion techniques and PFO closure are coming.
5. Other novel SHD interventions.

Therapy in SHD Including Valvular Heart Disease

1. Surgery has been the therapeutic gold standard.
2. Medical therapy has been limited and predominantly used to treat secondary complications rather than altering the primary pathophysiological process.
3. Transcatheter therapy has been limited to several relatively small patient groups, but that is starting to change...

Balloon Mitral Valvuloplasty
Class 1A Indication for Rheumatic Mitral Stenosis

1. Fused mitral commissures must be present
2. Not good for calcified annulus and leaflets
3. Uncommon in US, very common in India, China, etc.
4. Most frequent major complication – severe mitral regurgitation 5-6%
Isn’t Valvular Heart Disease Going Away?

Hasn’t Rheumatic Fever Been Eliminated from the US?

Clinically Significant Valvular Heart Disease is Becoming More Prevalent in the US

The Growth in the US Elderly Population
The Diversity of Elderly Patients

- Surgery therapy may not be feasible for many elderly patients with valve disease.
- How does the addition of new transcatheter therapies play out?
  - Assessing risks and benefits
  - Burden of treatment
  - Goals of the patient
  - Determination of patient preferences

Surge of Innovation for Unmet Clinical Needs

- Transcatheter valve replacement
- Transcatheter valve repair

FDA Approval of First Transcatheter Valve
Jan. 25, 2010
Medtronic Melody Pulmonary Valve
TAVR: Transcatheter Aortic Valve Replacement

The Technology and The Technique

- Bovine pericardium fashioned into heart valve leaflets and mounted inside a metal stent.
- Deployment of new valve pushes aside old valve.
- Delivery system and technique
  - Large caliper catheters
  - Coordinated team procedure often in hybrid OR
- General anesthesia for now

TAVR
Putting the Valve in: Transfemoral and Transapical Approaches
Valve Deployment

- TEE Probe
- Pigtail Catheter in Aorta
- SG Catheter in PA
- Pacer in RV
- Guide wire in LV

Senile or Calcific Aortic Stenosis

- Any Abnormality
- AVA 0.6 - 1.2 cm²
- AVA < 0.8 cm²

Natural History of Aortic Stenosis in 2013

- Latent Period
- Increasing obstruction, myocardial overload
- Symptoms
- Average Age Death

Adapted from Ross and Braunwald, Circulation 1968;38:N-61
At Least 30% of Patients with Severe Symptomatic AS are “Untreated”!

PARTNER Trial

Transcatheter Aortic-Valve Implantation for Aortic Stenosis in Patients Who Cannot Undergo Surgery

PARTNER Study Design
### Two Year All Cause Mortality

<table>
<thead>
<tr>
<th>Months</th>
<th>All Cause Mortality (%)</th>
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<tbody>
<tr>
<td>0</td>
<td>50.7%</td>
</tr>
<tr>
<td>6</td>
<td>43.3%</td>
</tr>
<tr>
<td>12</td>
<td>37.3%</td>
</tr>
<tr>
<td>24</td>
<td>30.7%</td>
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</tbody>
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#### NNT = 5.0 pts

#### HR [95% CI] = 0.57 [0.44, 0.75]

\[ \text{p (log rank)} < 0.0001 \]

### Quality of Life Evaluation

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Description/Role</th>
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| Kansas City Cardiomyopathy Questionnaire (KCCQ) | Heart Failure-specific QOL  
Domains: Symptoms, Physical Limitations, Quality of Life, Social Limitations  
Scores: 0-100 (higher = better) |
| SF-12                 | General physical and mental health  
Scores standardized such that mean=50, standard deviation=10 (higher = better) |
| EQ-5D (EuroQOL)       | Generic instrument for assessment of utilities and QALYs  
Scores: 0-1 (0=death; 1=perfect health) |

- Assessments performed by self-administered
- questionnaires at baseline, 1, 6, & 12 months

### The Team

_Providing Patients with an Experience They Rarely Experience_
Severity of Aortic Stenosis
Hemodynamic Definition

- **Mild** (area 1.5 cm², mean gradient less than 25 mm Hg, or jet velocity less than 3.0 m per second)
- **Moderate** (area 1.0 to 1.5 cm², mean gradient 25 to 40 mm Hg, or jet velocity 3.0 to 4.0 m per second)
- **Severe** (area less than 1.0 cm², mean gradient greater than 40 mm Hg, or jet velocity greater than 4.0 m per second).

Challenges to Transfemoral Insertion

- Vessels too small
- Prior Vascular Surgery
- Iliac Stenting
- Aortic occlusion

Categories of Patients with Severe Aortic Stenosis

- Operable AS Patients
  - **Low-Intermediate Risk**: 75%
  - **High Risk**: 10%
  - **Futile**: 10%
  - **Excessive Risk or Inoperable**: 5%
The STS Risk Calculator
Society of Thoracic Surgeons

*The Risk Calculator incorporates the STS risk models that are designed to serve as statistical tools to account for the impact of patient risk factors on operative mortality and morbidity.*


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85 African-American Woman with Severe Aortic stenosis, Normal EF, Single Vessel CAD, Insulin Requiring Diabetes, COPD and PVD

*What does the STS Risk Calculator Say?*

- Operation = Elective Surgical Aortic Valve Replacement and Single Vessel CABG
  - Risk of Mortality 9.2%
  - Morbidity or Mortality 43.7%
  - Long Length of Stay 34.5%
  - Short Length of Stay 5.3%
  - Permanent Stroke 2.5%
  - Prolonged Ventilation 35.4%
  - Renal Failure 20.1%
  - Reoperation 12.8%

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Risk Factors NOT Captured by Scoring Systems

- Liver disease/cirrhosis
- "Porcelain” aorta
- Chest irradiation
- Chest wall deformities
- Oxygen dependence
- Neurocognitive dysfunction
- "Debility” or “Frailty"
Explosion of TAVR in the USA
Over 230 Hospitals Have Programs

Who Shouldn’t Get TAVR
- Don’t want it
- Moderate to Severe Dementia (? Unclear cutoff)
- Competing comorbidities
- Multi-organ failure
- AS isn’t major problem
- Won’t make it two years due to other causes

Key Complications of TAVR
- Stroke
- Bleeding
- Vascular Complications
- Paravalvular Leak
- Need for permanent pacemaker
- ? Valve durability
Take Home Messages with TAVR

1. It is FDA approved for patients with excessive risk or high risk for surgical AVR.
2. It is restricted to centers with comprehensive heart valve programs, special facilities, and skills.
   - Minimizing major complications and caring for fragile patients
3. Surgical AVR remains an excellent therapy for most patients with AS.
4. Patient evaluation for TAVR/Surgical AVR is standardized, comprehensive, and includes defining the risks and benefits for the individual patient.
5. TAVR will rapidly evolve with new technologies in the next 5 years but valve durability will need to be documented before treatment expands to lower risk and younger patients.

What is That Thing?

Secundum ASD in Adults

Key Points

- It shortens lifespan
  - The earlier the “fix” more normalization in life span and reversal of chamber enlargement, reversal of PHTN
- Only 50% are discovered during childhood
- Discovery in adulthood requires clinical acumen and suspicion by PCPs
- Transcatheter closure with excellent outcomes has emerged as a suitable and preferred treatment for the majority of adult secundum ASDs in experienced centers.
  - Patients prefer short recovery period, lack of chest scar, and ability to resume active lifestyle quickly
Clinical Presentation Modes of ASD in the Adult

1. Dyspnea, fatigue, exercise intolerance
2. Palpitations, atrial arrhythmias
3. Incidental: cardiomegaly, heart murmur, unexplained RVH or right axis deviation on ECG
4. Paradoxical embolism

ECG in ASD

Right axis deviation and rsR' in V1

ASD Complicated by PHNTN with marked RVH

CXR

- Cardiomegaly
- PA enlargement
- Lateral showing retrosternal fullness suggestive of RVE
Echocardiography

1. Transthoracic (TTE): RVE, RAE, LAE, estimated RV systolic pressure
2. Transesophageal (TEE): Clarifies size, shape, degree of left to right shunting, and whether device closure is appropriate

Who Should Have ASD Closure?
Warnes et al. ACC/AHA 2008 Guidelines for Adults With CHD

• Class I
  – Closure of an ASD either percutaneously or surgically is indicated for right atrial and RV enlargement with or without symptoms.
  (Level of Evidence: B)

ASD and Pulmonary Hypertension
Impact on ASD Closure Therapy

<table>
<thead>
<tr>
<th>Normal or Mildly Elevated PA Pressures</th>
<th>Severe, Elevated PA Pressures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Majority of Adult Secundum ASD patient</td>
<td>Moderate to severe PHTN but not Eisenmenger’s syndrome</td>
</tr>
<tr>
<td>Low Risk of Closure</td>
<td>Safe to Closure?</td>
</tr>
<tr>
<td>Will have normalization of pressure</td>
<td>Reversibility?</td>
</tr>
<tr>
<td>RVE may normalize depending on age when closure occurs</td>
<td>Eisenmenger’s Syndrome</td>
</tr>
<tr>
<td>Cyanotic from R to L shunting</td>
<td>Severe PHTN</td>
</tr>
</tbody>
</table>
| Too Late for Closure | }
Indications for Closure of Atrial Septal Defect
Warnes et al ACC/AHA 2008 Guidelines for Adults With CHD

- Small ASDs with a diameter of less than 5 mm and no evidence of RV volume overload do not impact the natural history of the individual and thus may not require closure unless associated with paradoxical embolism.

Two FDA Approved ASD Transcatheter Delivered Closure Devices

- AGA Amplatzer ASO Device
- Gore Helex Device

Deployment

- Over 400 secundum cases at UCH successfully closed
  - Simple to complex
- Major complications
  - No procedure death, MI, or stroke
  - Embolized device unable to retrieve x 2
  - Post-procedure issues
Transcatheter ASD Closure

- Feasible for approximately 90% of patients discovered to have an ASD in adulthood
  - Surgery remains suitable for some patients
- Procedure takes 1-2 hours, overnight stay, and quick recovery.
- Dual antiplatelet therapy standard of care for 3-6 months.
- Post-procedure issues: SVT (5%), atypical chest pain, nickel allergy, very rare device erosion (3/1000).
- Follow-up echo should show resolution of RVE but atrial enlargement persists.

The Central Claim

- Patent foramen ovale is not always an innocent remnant of the fetal circulation.

In utero the PFO is open in all and allows oxygenated blood to reach the systemic circulation

In 20-25% of adults have a PFO and a subset have large PFO's with continuous or intermittent right to left shunting
PFO Pathophysiology
Its presence enables right to left atrial shunting with a plethora of material each with unique clinical consequences

- Paradoxical emboli: Acute and chronic effects especially stroke
- Substances that trigger migraine.
- Nitrogen bubbles during ascent of scuba divers – decompression sickness
- Volumetrically enough blood to cause systemic oxygen desaturation
- Fat embolism

Pathophysiology of PFO and Paradoxical Embolism
- Normal appearing atrial septum
- Agitated saline study demonstrating right to left shunting through the PFO
- Blood clot passing through the PFO becoming a paradoxical embolism

PFO Closure
RESPECT Efficacy Analyses
46.6%-72.7% risk reduction of stroke in favor of device

- Totality of Evidence
  46.6% - 72.7% risk reduction of stroke in favor of device

- Primary Endpoint Analyses – ITT Cohort
  
<table>
<thead>
<tr>
<th>Method</th>
<th>Risk Reduction</th>
<th>P-value</th>
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<tr>
<td>Intent To Treat</td>
<td>50.8%</td>
<td>0.083</td>
</tr>
<tr>
<td>Per Protocol</td>
<td>63.4%</td>
<td>0.032</td>
</tr>
<tr>
<td>As Treated</td>
<td>72.7%</td>
<td>0.007</td>
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P-values ITT Raw Count are calculated using Fisher’s Exact Test; all other P-values are calculated Log-Rank Test.

Conclusions

• While off-label device closure of PFO is performed, the FDA has yet to approve a device specifically for PFO.

• Randomized clinical trials have had multiple challenges but there appears to be a group of patients likely to have recurrent stroke risk reduction that is greater with PFO closure. – Is level of evidence adequate for FDA approval?

• Combined neurology-cardiology evaluation recommended in a specialized center, i.e. a PFO clinic.
Percutaneous Mitral Valve Repair
With The Evolve Clip
Clinical Trials

• EVEREST 1: Completed
• EVEREST 2: ACC 2010
• REALISM: 2008-2012
  – Ongoing access to device for same group of patients as in EVEREST 2

MitraClip Concepts

• Facilitates proper leaflet coaptation
  – Degenerative MR - Anchors flail and prolapsed
  – Functional MR - Coapts tethered leaflets

• Creates tissue bridge between A2-P2
  – Limits dilatation of annulus
    • Septal-lateral (A-P) dimension
  – Supports durability of repair

EII RCT: Safety & Effectiveness Endpoints
Intention to Treat Cohort

Safety
Major Adverse Events
30 days

Device Group, n=96
15.0%
Control Group, n=94
47.9%
P<0.0001

Effectiveness
Clinical Success Rate
12 months

Device Group, n=92
66.9%
Control Group, n=91
74.2%
P<0.0005

Met superiority hypothesis
• Pre-specified margin = 12%
• Observed difference = 32.9%
• 97.5% LEB = 20.7%

Met non-inferiority hypothesis
• Pre-specified margin = 25%
• Observed difference = 7.3%
• 95% LEB = 17.8%

On August 20, 2007 This 94 Year Old Man with Refractory CHF and Near Death Received a MitraClip™
High-Risk Registry of EVEREST 2

- "I really feel like a newborn man."
- He recounted a recent week in which he went to a Sky Sox game, attended a horse show, hiked Cheyenne Mountain Park, played cards with friends, and attended a concert.
- NYHA Class 1 in clinic last month

Mitral Clip Therapy for Mitral Regurgitation

- Remains investigative in 2013 but has potential for FDA approval for inoperable patients soon.
- Provides a new safe and reasonably effective treatment option which is especially needed in high-surgical risk patients.
- Caveats:
  - Advanced procedure that requires specialized team
  - It is applicable to a subset of MR patients with specific anatomical characteristics

Other In-Hospital Complications in SHD Interventions

- Tamponade:
  - Usually immediate but may be delayed
  - Hypotension
  - Echocardiography
- Device Embolization
  - Ectopy
  - Hemodynamic changes
- Bleeding
  - Access site
  - Retroperitoneal – hypotension and pain
Regionalization of Services
UC Denver Valve Program

• Milestones:
  – Balloon mitral commissurotomy program initiated in 1996
  – MitraClip investigative program initiated in 2004
  – Paravalvular leak program: 2007
  – Melody Transcatheter Valve: 2010
  – TAVR: First patient March 2012: Over 50 patients treated with 30 day mortality of 1.9% and major stroke rate of 0%.
  – PARTNER 2 clinical trial: 2012-
• More than 800 patients have undergone transcatheter therapy for mitral stenosis, aortic stenosis, pulmonary stenosis, tricuspid stenosis, paravalvular leaks, and mitral regurgitation.
• The UC Denver team:
  – Surgical and specialized interventional groups
  – Advanced imaging, heart failure, peripheral/aortic intervention, and EP services
  – Percutaneous LV assist devices, VAD/transplant backup, hybrid OR.

Conclusions

• The revolution in structural heart disease interventions has begun and its impact on patient care will be similar to PCI.
• You need to be familiar with these therapies in terms of patient selection, diagnostic evaluation, the nature of the intervention, and potential complications.
• Some therapies impact on very common clinical issues including aortic stenosis, mitral regurgitation, and stroke prevention in atrial fibrillation.

Questions

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