Innovation & The Future of Heart Valve Disease Treatment
Lisa M. Tate

Interim Executive Director, Heart Valve Voice
US

Lisa M. Tate is a long-time health advocate, having held leadership positions for patient organizations, a hospital association, and a medical society. For the past ten years, she has focused on cardiovascular issues. As CEO of WomenHeart, the National Coalition for Heart Disease, she more than tripled the organization’s revenue, enabling WomenHeart to reach millions more women. Currently Lisa has her own patient advocacy consulting firm, Health Futures Consulting: *Putting Patients at the Center.*
Heart Valve Voice US is the only patient-led organization in the country that exclusively focuses on improving the diagnosis, treatment and management of heart valve disease.
Heart Valve Voice US

- Provides a voice for heart valve patients to improve access to the right treatment at the right time
- Raises awareness of symptoms and severity of heart valve disease, particularly in at-risk and underserved populations
- Educates patients so they can partner with their physicians in decision-making regarding their care
- Advocates for policy changes to ensure optimal treatment of heart valve, e.g., Medicare, research funding
- Partners with other organization to encourage them to focus on HVD
Susan Strong

**Director of Communications and Patient Engagement, Heart Valve Voice US**

Susan Strong is Director of Communications and Patient Engagement for Heart Valve Voice US. She was the founding President of the Board of Directors and is a passionate advocate for heart valve patients. In addition to her role at Heart Valve Voice US, Strong serves as an American Heart Association Heart Valve Ambassador and is actively involved as a patient stakeholder in clinical research.
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Professor of Surgery

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Innovations and the Future of Valve Disease Treatment

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Disclosures

- Institutional Grant/Research Support
  - Philips Medical Systems
  - Edwards Lifesciences
  - Medtronic Corp
  - Abbott
Outline

• Update on Transcatheter Aortic Valve Replacement
  – Emerging Indications for TAVR

• Update on Mitral Valve Technologies
  – MitraClip Indications
  – New Approaches

• Emerging Tricuspid Valve Therapies

• Q and A
Background

• Surgical Valve Replacement has been the gold standard for treatment of severe valve stenosis since the 1960’s
• In 2011, the STS database reported over 48,000 patients underwent surgical mitral and aortic valve replacement in the US
• Median mortality rates for isolated surgical valve replacement in the TAVR era in the STS database in 2016:
  – 2.2 % for AVR
  – 4.4% for MVR
• Unfortunately, as our population ages, with more co-morbid conditions, the surgical risk is increasing!

US Population Projection by Age Group: US Census Bureau

Figures for projections from 2010 through 2050 are from: Table 12. Projections of the Population by Age and Sex for the United States: 2010 to 2050 (NP2008-T12), Population Division, U.S. Census Bureau; Release Date: August 14, 2008
Valvular Heart Disease Increases with Age—
Pooled Echo Data from ARIC/CARDIA/CHS

Nkomo VT et al. Lancet 2006, 368;1005-11
Aortic Stenosis

Normal

Degenerative
Calcified

Bicuspid

Rheumatic
Factors Associated with Increased Risk for Surgical Aortic Valve Replacement

Clinical
- Prior Sternotomy
- Female gender
- Renal dysfunction
- Diabetes
- Moderate to severe COPD
- Low EF
- NYHA Class IV
- Cerebrovascular disease
- Immunosuppression

Anatomic
- Porcelain aorta
- Prior radiation
- Bypass graft course under sternum
- Prior sternectomy

Non-Traditional
- Frailty
- High operative risk
  - Cirrhosis
  - Pulmonary Hypertension
Surgical AVR Risk Categories

(risk is a continuum)

Operable AS patients

Low-Intermediate Risk

High Risk

Inoperable

Too Sick

<3%  3-8%  >8%

90%  10%

Current FDA Approval
PARTNER 3 and Medtronic
Low Risk Trials

Primary Endpoint
Death, Stroke or Rehospitalization

Number at risk:
- Surgery: 454, 408, 390, 381, 377, 374
- TAVR: 496, 475, 467, 462, 456, 451

Death, Stroke, or Rehosp (%)
- Surgery: 9.3%, 4.2%, 4.2%, 4.2%, 4.2%, 4.2%
- TAVR: 15.1%, 8.5%, 8.5%, 8.5%, 8.5%, 8.5%

P non-inferiority < 0.001
P superiority = 0.001

Upper 95% CI of risk diff = -2.5%

HR [95% CI] = 0.54 [0.37, 0.79]

Primary Endpoint

Death, Disabling Stroke and Heart Failure Hospitalizations to 1 Year

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<th>Composite Rates</th>
<th>TAVR</th>
<th>SAVR</th>
<th>Difference</th>
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TAVR in Low Risk Patients—Will be approved in 2019!
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

Primary Endpoint (superiority): 2-year composite of all-cause mortality, all strokes, and repeat hospitalizations (CV)
TAVR UNLOAD Trial: Study Design
(600 patients, 1:1 Randomized)

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

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

TAVR UNLOAD Trial
International Multicenter Randomized

TAVR + OHFT

OHFT Alone

Reduced AFTERLOAD
Improved LV systolic and diastolic function
TAVR for Aortic Regurgitation

Dedicated Valve for NVAR--JenaValve

- Nitinol self expanding
- Three feelers for sinus stabilization, clips hold in place leaflets
- Recapturable, repositionable
- 23, 25 and 27 mm Valve
- CE Mark in 2013
- Gen 2 Device CE Mark Study underway as of 6/2018
- Only valve approved for NVAR
The Unique Challenges and Opportunities for Treating Mitral Valve Disease with Catheter Based Therapy

MITRAL VALVE: THE NEXT FRONTIER
Mitral Valve Disease

Rheumatic MS and MR

Functional

Degenerative

Normal

“Secondary”

“Primary”
Mitral Valve Disease Is Increasing Faster Than Aortic Valve Disease!

Nkomo VT et al. *Lancet* 2006, 368;1005-11
Key Issues

• Operative risk for MV replacement is about double that of AVR
• Patients with MR have more co-morbid conditions making them higher risk at baseline
• Patients with Functional MR don’t get surgical MVR
A Simple Method: Surgical Edge-to-Edge Mitral Repair

- Approximate mid-sections of A2 and P2
- Suture in the center, creating a double orifice
- >600 procedures published in peer review journals

Treatment of Functional Mitral Regurgitation

The COAPT Trial
Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation

A parallel-controlled, open-label, multicenter trial in ~610 patients with heart failure and moderate-to-severe (3+) or severe (4+) secondary MR who remained symptomatic despite maximally-tolerated GDMT

Randomize 1:1*

MitraClip + GDMT
N=305

GDMT alone
N=305

*Stratified by cardiomyopathy etiology (ischemic vs. non-ischemic) and site

Slide From Stone, et al. COAPT Trial Presentation, TCT 2018
COAPT Trial Primary Endpoint

Primary Effectiveness Endpoint
All Hospitalizations for HF within 24 months

- MitraClip + GDMT
- GDMT alone

Cumulative HF Hospitalizations (n)

Time After Randomization (Months)

HR (95% CI) = 0.53 [0.40-0.70]
P<0.001

No. at Risk:
MitraClip 362 286 269 253 236 191 178 161 124
GDMT 312 294 271 245 219 176 145 121 88

Median (25%, 75%) FU = 19.1 (17.9, 24.0) mos.
Transcatheter Mitral Valve Repair in Early Feasibility Studies in the US

- MitraClip NTR
- MitraClip XTR (+5mm*)
- MitraClip XTR (Abbott)
- CARILLON Annuloplasty System (Cardiac Dimensions)
- CardioBand Annuloplasty System (Edwards)
- Millipede Annuloplasty System

Pascal Spacer (Edwards)
CLASP Clinical Trial
Cardioband Trial

Edwards Cardioband System ACTIVE Pivotal Clinical Trial (ACTIVE) (ACTIVE)

ClinicalTrials.gov Identifier: NCT00103735

Recruitment Status: Active, not recruiting
First Posted: January 11, 2017
Last Updated Posted: March 10, 2019

Sponsor:
Edwards Lifesciences

Information provided by (Responsible Party):
Edwards Lifesciences
Transcatheter Mitral Valve Therapies Approved for Early Feasibility Study in US

Transapical
- Tendyne (Abbott)
- Intrepid TMVI (Medtronic)
- Tiara (Neovasc)

Transfemoral
- CardiaQ (Edwards)
- Highlife M3 (Edwards)
- Caisson (LivaNova)
Anatomic Challenges Facing Transcatheter Mitral Valve Replacement (TMVR)
Technical Challenges With TMVR

- Current generation delivery systems are very large—Transapical route of delivery
- Different complications than TAVR
  - LVOT obstruction, conduction system abnormalities circumflex artery obstruction
- Impact on the LV function
- Prosthetic related events
  - thrombosis, endocarditis, embolization, paravalvular regurgitation
- Need for ongoing anticoagulation

Tendyne Summit Trial
Tricuspid Valve Disease—

- Currently high risk operation with open surgical intervention
- Percutaneous approaches challenging due to anatomy
- Imaging of the tricuspid valve for percutaneous interventions is difficult

Trends and Outcomes of Tricuspid Valve Surgery in North America: An Analysis of More Than 50,000 Patients From The Society of Thoracic Surgeons Database

Arman Kilic, MD, Paramita Saha-Chaudhuri, PhD, J. Scott Rankin, MD, and John V. Conte, MD
Division of Cardiac Surgery, Johns Hopkins Hospital, Baltimore, Maryland; Department of Biostatistics and Bioinformatics, Duke University School of Medicine, Durham, North Carolina and Centennial Medical Center and Vanderbilt University, Nashville, Tennessee

- Years 2000-2010
  - Procedures 54,375
  - 4,943/year
  - Concomitant 46,593 (85.7%)
  - Isolated 7,782
  - 707/year
  - 88.9% Repair
  - 30 day mortality 9.6%

![Operative Mortality Chart]
Tricuspid Valve Repair and Replacement

Tricuspid Valve Interventions—
All Investigational currently
Conclusions

• TAVR is currently FDA approved for treatment of inoperable, high risk and intermediate risk patients with symptomatic aortic stenosis
  – Including valve in valve and patients with bicuspid aortic valves

• TAVR has been demonstrated to be equivalent or superior to SAVR now in low surgical risk patients
  – Expect FDA approval soon!

• TAVR being evaluated in:
  – Asymptomatic severe AS
  – Moderate AS with LV dysfunction
  – Aortic regurgitation
  – New and next generation valve technologies
Conclusions (cont)

• Mitral valve repair/replacement timeline will be much longer than TAVR due to the complexity of the mitral valve
  – Transcatheter Mitral Valve Repair with MitraClip is only FDA approved for high surgical risk patients (STS>8%) with degenerative MR
• The COAPT Trial has established the superiority of MitraClip+GDMT to GDMT alone in patients with functional MR
  – Expect FDA approval soon!
• Transcatheter mitral valve replacement and repair has many promising technologies
  – Many first-in-human studies underway in the US.
• Tricuspid valve approaches are in their infancy but are moving forward quickly
For Information about Clinical Trials for Your Condition, see:

https://www.clinicaltrials.gov/

https://www.antidote.me/
Thank You!