The CoreValve US Pivotal Trial

Ted Lystig, Ph.D.
Distinguished Statistician
Medtronic, Inc.

January 29, 2014
Medtronic CoreValve – What is it?

Valve
Self-expanding Nitinol frame with porcine pericardial valve

Loading System
Disposable cones and tubes used to compress the valve

Delivery Catheter
18Fr profile delivery catheter system with AccuTrak® stability layer
Study Purpose: To evaluate the safety and efficacy of the CoreValve THV for the treatment of patients with symptomatic severe aortic stenosis in whom the predicted risk of operative mortality or serious, irreversible morbidity was 50% or greater at 30 days.

Risk Determined by: Two Clinical Site Cardiac Surgeons and One Interventional Cardiologist.

Risk Confirmed by: Two Screening Committee Cardiac Surgeons and One Interventional Cardiologist.

Primary Endpoint: All Cause Mortality or Major Stroke at 12 Months.
Study Administration

Co-Principal Investigators
Jeffrey Popma, BIDMC, Boston
David Adams, Mt. Sinai, New York

Steering Committee
CS’s: Michael Reardon, G. Michael Deeb, Joseph Coselli, David Adams, Tom Gleason
IC’s: James Hermiller, Steven Yakubov, Maurice Buchbinder, Jeffrey Popma
Consultants: Blasé Carabello, Patrick Serruys

Data & Safety Monitoring Board
Chair: David Faxon, Brigham and Women’s Hospital

ECG Core Laboratory
Chair: Peter Zimetbaum, HCRI

Quality of Life and Cost-Effective Assessments
Chair: David J. Cohen, Mid-America Heart Institute
Matt Reynolds, HCRI

Pathology Core Laboratory
Chair: Renu Virmani, CV Path

Screening Committee
Chair: Michael Reardon, David Adams, John Conte, G. Michael Deeb, Tom Gleason, Jeffrey Popma, Steven Yakubov

Sponsor
Medtronic, Inc.
Inclusion and Exclusion Criteria

Inclusion Criteria:

• Severe aortic stenosis: AVA ≤ 0.8 cm² or AVAI ≤ 0.5 cm²/m² AND mean gradient > 40 mm Hg or peak velocity > 4 m/sec at rest or with dobutamine stress (if LVEF < 50%)
• NYHA functional class II or greater

Exclusion Criteria (selected):

• Recent active GI bleed (3 mos), stroke (6 mos), or MI (30 days)
• Creatinine clearance < 20 mL/min
• Significant untreated coronary artery disease
• LVEF < 20%
• Life expectancy < 1 year due to co-morbidities
Our 1st Challenge: The TAVR Landscape Changed

- October 2010 TCT - TAVR has demonstrated **significant survival improvements** compared to medical management in inoperable patients. Result - **Clinical Equipoise No Longer Existed**

Graph:
- **Standard Rx** vs **TAVI**
- All-cause mortality (%)
- Months
- Δ at 1 yr = 20.0%
- NNT = 5.0 pts

Leon TCT 2010 LBCT
An objective performance goal (OPG) was used to estimate the risk of all-cause mortality or major stroke in patients treated with standard therapy.

OPG constructed from:

- Meta-analysis of 5 contemporary balloon valvuloplasty series → random effects meta-analytic all-cause mortality or major stroke rate at 12 months = 42.7% (95% CI 34.0%-51.4%)

- 12-Month PARTNER B all-cause mortality or major stroke rate of 50.3% with a corresponding 95% lower confidence bound of 43.0%
US CoreValve Extreme Risk Iliofemoral Study

CoreValve US Pivotal Trials

- Extreme Risk
  - Assessment: iliofemoral access
    - Yes
      - CoreValve Iliofemoral
        - N=487
    - No
      - CoreValve Non-Iliofemoral
        - N=147

- High Risk
  - Randomization 1:1
    - Vs.
      - CoreValve
      - SAVR

TVT 2013 Preliminary Analysis
Study Disposition

Screening Committee Approved
N=737

Subjects Not Enrolled
N=18

Subject Enrolled
N=719

Roll-in Subjects N=63
23 mm Subjects N=22

ITT Population Illofemoral
N=487

ITT Population Non-Illiofemoral
N=147

Exit Prior to Procedure
N=11

As Treated Population
IIlofemoral N=471

No Iliofemoral Access N=5

Implanted IIlofemoral Population
N=470

Non Implanted
N=1

Per Protocol Population
N=455

Did not meet the per-protocol
definition N=15
RISK-BASED MONITORING

Is Risk-Based Monitoring Risky Business?

Bio Research Central Summit

November 2013

Margaret F. Fay, Ph.D., RN, CCRC, CRA
Medtronic Clinical Research Institute
How Do You Implement RBM?

Implementation requires

- Assembly of a core team
- Identification of known risks (sponsor, site, study)
- Projection of possible unforeseen risks
- Assignment of weighted value to each risk identified
- Risk elimination/mitigation as far as reasonably practicable
- Establishing acceptable tolerance levels for various events
- Identify an event response for residual risks
- Escalation plan for monitoring action items
RBM Monitoring Future State

Standardize processes, systems, tools and data integration

**Current State**

1. Manual (mostly methods)
2. Minimal data integration
3. Minimal trending (x trials)
4. Aging report

**Future State**

1. Automated methods, workflow, standard medical coding, signal alerts
2. Full integration across trial lifecycle (from event to final state)
3. Consolidated data for analysis and reporting
4. KPI, KRI, trend analysis of variances
Identify the Right Monitoring Actions and Save Time and Money

- Reduce trial delays
- Increase quality of data
- Ensure compliance through proactive responsiveness
- Increase productivity and save resources
- Minimize risk of submission errors
Study Compliance

Clinical Assessments

- Baseline
  - N=471
  - 100% Follow-up (n=471/471)

- 1-Month
  - N=435
  - 98.2% Follow-up (n=427/435)

- 1-Year
  - N=355
  - 98.9% Follow-up (n=351/355)

Echocardiographic Assessments

- 100% Echo Performed (n=471/471)

- 96.6% Echo Performed (n=420/435)

- 91.0% Echo Performed (n=323/355)
Primary Endpoint

All Cause Mortality or Major Stroke

- 9.3% (6.7, 12.0) at 1 year
- 25.5% (21.6, 29.4) at 12 months

P < 0.0001

Performance Goal = 43%
## Secondary Endpoints

<table>
<thead>
<tr>
<th>Events*</th>
<th>1 Month</th>
<th>1 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Stroke, %</td>
<td>3.9</td>
<td>6.7</td>
</tr>
<tr>
<td>Major, %</td>
<td>2.4</td>
<td>4.1</td>
</tr>
<tr>
<td>Minor, %</td>
<td>1.7</td>
<td>3.1</td>
</tr>
<tr>
<td>Myocardial Infarction, %</td>
<td>1.3</td>
<td>2.0</td>
</tr>
<tr>
<td>Reintervention, %</td>
<td>1.3</td>
<td>2.0</td>
</tr>
<tr>
<td>VARC Bleeding, %</td>
<td>35.1</td>
<td>41.4</td>
</tr>
<tr>
<td>Life Threatening or Disabling, %</td>
<td>11.7</td>
<td>16.6</td>
</tr>
<tr>
<td>Major, %</td>
<td>24.1</td>
<td>27.6</td>
</tr>
<tr>
<td>Major Vascular Complications, %</td>
<td>8.3</td>
<td>8.5</td>
</tr>
<tr>
<td>Permanent Pacemaker Implant, %</td>
<td>22.2</td>
<td>27.1</td>
</tr>
<tr>
<td>Per ACC Guidelines, %</td>
<td>17.4</td>
<td>19.9</td>
</tr>
</tbody>
</table>

* Percentages obtained from Kaplan Meier estimates
CoreValve US Pivotal Trial
Extreme Risk Iliofemoral
Study Results

Jeffrey J. Popma, MD
On Behalf of the CoreValve US Clinical Investigators
CoreValve US Pivotal Trial
Extreme Risk Iliofemoral Study Results

CoreValve US Pivotal Extreme Risk Non-Iliofemoral Cohort

David H. Adams, MD
Co-Principal Investigator, on Behalf of the
CoreValve US Clinical Investigators
CoreValve US Pivotal Trial
Extreme Risk Iliofemoral
Study Results

CoreValve US Pivotal Extreme Risk
Non-Iliofemoral Cohort

Echocardiographic Results in the
CoreValve U.S. Extreme Risk Study
Hemodynamics and Aortic Regurgitation

Jae Oh, MD, FAHA, FACC, FASE
On Behalf of the CoreValve US Clinical Investigators
CoreValve US Pivotal Trial
Extreme Risk Iliofemoral Study Results

CoreValve US Pivotal Extreme Risk Non-Iliofemoral Cohort

Echocardiographic Results in the CoreValve U.S. Extreme Risk Study
Hemodynamics and Aortic Regurgitation
A Critical Analysis of Functional Improvement after TAVR in the CoreValve US Extreme Risk Study

David J. Cohen, M.D., M.Sc.
On Behalf of the CoreValve US Clinical Investigators
Pre-Procedural Predictors of All-Cause Mortality and Major Stroke in US CoreValve Pivotal Trial

Non-TAVR Patients

Thomas Gleason, MD
On Behalf of the CoreValve US Clinical Investigators

CoreValve U.S. Extreme Risk Study Hemodynamics and Aortic Regurgitation

A Critical Analysis of Functional Improvement after TAVR in the CoreValve US Extreme Risk Study

David J. Cohen, M.D., M.Sc.
On Behalf of the CoreValve US Clinical Investigators
Pre-Procedure Predictors of All-Cause Mortality and Major Stroke in US CoreValve Pivotal Trial

CoreValve US Pivotal Extreme Risk Continued Access Study Results

Steven J. Yakubov, MD
On Behalf of the CoreValve US Clinical Investigators

Improvement after TAVR in the CoreValve US Extreme Risk Study

David J. Cohen, M.D., M.Sc.
On Behalf of the CoreValve US Clinical Investigators
Pre-Procedural Predictors of All-Cause Mortality and Major Stroke in US CoreValve Pivotal Trial

CoreValve US Pivotal Extreme Risk Study Results

Procedural Outcomes in the US CoreValve Extreme Risk Trial

Michael Reardon, MD
On Behalf of the CoreValve US Clinical Investigators

David J. Cohen, M.D., M.Sc.
On Behalf of the CoreValve US Clinical Investigators
CoreValve US Pivotal Trial
Extremely High-Risk
Study Results

Pre-Procedural Predictors of All-Cause Mortality and Major Stroke in US CoreValve Pivotal Trial

CoreValve US Pivotal Extreme Risk Continued Access Study Results

Procedural Outcomes in the US CoreValve Extreme Risk Trial

Vascular and Bleeding Complications

James Hermiller, MD
On Behalf of the CoreValve US Clinical Investigators

On Behalf of the CoreValve US Clinical Investigators
Perspective on 1 Year Mortality

CoreValve US Pivotal

All Cause Mortality Standard Rx*

TCT 2013 Non-Iliofemoral Access

*Leon MB, et al. NEJM 2010;363:1597

Extreme Risk Study | NIF 16
New Cures For Old Ailments

Some of our most common chronic illnesses will get fresh therapies

BY ALICE PARK

The era of blockbuster drugs may be fading, but that doesn’t mean medical innovation is dead. Here are treatments coming this year:

» A valve that can fix your heart From Medtronic, this device replaces failing valves that could block blood flow in heart vessels, which would otherwise be fatal in half of patients with the condition. The CoreValve system has been tested in 50,000 patients outside the U.S.

» Pills that stop Hep C The first oral treatments for a viral infection that causes inflammation of the liver in 3.2 million Americans, simprevir and sofosbuvir were approved by the U.S. Food and Drug Administration in October. The drugs, taken in combination with an existing therapy such as interferon or ribavirin, shorten treatment from one year to 12 weeks and can cure up to 86% of cases.

» A vaccine for malaria The European Medicines Agency and the FDA are reviewing data on Mosquirix, a vaccine from GlaxoSmithKline (GSK) that is the first against a parasite and the first to protect against malaria, which affects 219 million people worldwide. The shot can lower risk of the deadly disease by 46% among children where the parasite is endemic.

» A simpler diabetes treatment Daily pills may become a thing of the past for Type 2 diabetics if GSK’s albiglutide is approved. The once-a-week medication hampers the glucagon receptor and lowers glucose production by the liver. Similar drugs out now need to be taken up to twice a day.

» A better breast-cancer drug Pfizer’s Herceptin and Tykerb already tackle the 30% of breast cancers that contain HER2 proteins; but many tumors become resistant to the drugs. Pfizer’s forthcoming dacomitinib targets multiple forms of HER2, which could make resistance less likely.
Thank you!

theodore.lystig@medtronic.com