The CoreValve US Pivotal Trial

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

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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

Echo Core Laboratory
- Chair: Jae Oh, Mayo Clinic

Rotational X-ray Core Laboratory
- Chair: Philippe Genereux, CRF

Clinical Events Committee
- Chair: Donald Cutlip, HCRI

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: $AVA \leq 0.8 \text{ cm}^2$ or $AVAI \leq 0.5 \text{ cm}^2/\text{m}^2$ AND mean gradient $> 40 \text{ mm Hg}$ or peak velocity $> 4 \text{ m/sec}$ 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 $< 20 \text{ mL/min}$
- Significant untreated coronary artery disease
- LVEF $< 20\%$
- Life expectancy $< 1 \text{ year}$ due to co-morbidities

31 Exclusion criteria in total
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 showing survival improvements](attachment:image.png)

\[ \Delta \text{ at 1 yr} = 20.0\% \]
\[ \text{NNT} = 5.0 \text{ pts} \]

A Preview of the Extreme Risk US CoreValve Registry

Jeffrey J. Popma, MD
Professor of Medicine
Harvard Medical School
Director, Interventional Cardiology
Beth Israel Deaconess Medical Center
Boston, MA
Objective Performance Goal

- 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%
Study Disposition

Screening Committee Approved
N=737

Subject Enrolled
N=719

Subjects Not Enrolled
N=18

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

ITT Population Iliofemoral
N=487

ITT Population Non-Iliofemoral
N=147

Exited Prior to Procedure
N=11

No Iliofemoral Access N=5

As Treated Population
Iliofemoral N=471

Implanted Iliofemoral 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**

**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

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**Standardize processes, systems, tools and data integration**

**Field Monitor**
- Data Entry
- Central Monitor

**Clinical OC • EDC • Systems**
- SDV
- SDR
- AE’s
- MAI’s

**KRI KPI**
- Event Alerts

**Flag Response Centralized Coding**
- Monitoring Review
- YES
- NO

**Action Required**
- Document Management System
- NO
- Clinical Reporting

**Action Indicated**
- Event Closed
- Study Team Notification
- Further Action Indicated
- No Further Action
- Closed

**Query Generated**
- Site Contact
- Visit Scheduled

**Work from Home**

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Identify the Right Monitoring Actions and Save Time and Money

Focus on Key Data

Key Performance Metrics Across Entire Study

= Identify the Right Monitoring Intensity

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

70% - All Cause Mortality or Major Stroke

% 60% - 

Goal

S 40% - 

£ 30% M

2 3 20% 4 9-3'%! o

3 [6.7,12.0] 25.5%

S tou [21.6,29.4]

P < 0.0001

Performance Goal = 43%

9.3%

[6.7,12.0]

25.5%

[21.6,29.4]
## 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
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

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

CoreValve U.S. Extreme Risk Study
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CoreValve US Pivotal Extreme Risk Continued Access Study Results

Improvement after TAVR in the CoreValve US Extreme Risk Study

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

David J. Cohen, M.D., M.Sc.
On Behalf of the CoreValve US Clinical Investigators
Continued Access Study Results

Procedural Outcomes in the US CoreValve Extreme Risk Trial

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

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CoreValve US Pivotal Extreme Risk
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CoreValve Extreme Risk Trial

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Jae O. Huh, M.D.
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Medtronic
Perspective on 1 Year Mortality

CoreValve US Pivotal

All Cause Mortality Standard Rx*

- Non Iliofemoral
- Iliofemoral

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

TCT 2013 Non-Iliofemoral Access

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, simeprevir 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 88% 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 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.

▪ Autopilot In September, NASA will conduct an unarmed test flight of Orion, a craft designed to take humanity into deep space.
Thank you!

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