A Prospective, Randomised Investigation of a Novel Transcatheter Aortic Valve Implantation System: The REPRISE III Trial

Ted E. Feldman, MD

Evanston Hospital, Cardiology Division, Evanston, IL, USA


on behalf of the REPRISE III Investigators
Potential Conflicts of Interest

Speaker: Ted E. Feldman, MD

I have the following potential conflicts of interest to report:

• Institutional grant/research support: Abbott, Boston Scientific, Edwards Lifesciences

• Honoraria/consultation fees: Abbott, Boston Scientific, Edwards Lifesciences

The REPRISE III trial is sponsored and funded by Boston Scientific Corporation.
Background

- Transcatheter aortic valve implantation (TAVI): Well-established alternative to surgery for patients with severe aortic stenosis
- Current TAVI limitations include: Suboptimal deployment & paravalvular leak
- Lotus Valve System: Fully repositionable & retrievable TAVI device; Adaptive Seal to minimise PVL

- Controlled mechanical expansion; rapid pacing not needed during deployment
- Early valve function; haemodynamic stability during implantation
- Complete assessment before release; reposition/retrieve if not acceptable
REPRISE III Trial Characteristics

**DESIGN**

- Global, prospective, multicentre, randomised, controlled, noninferiority trial to compare safety & effectiveness with the Lotus valve versus a self-expanding TAVI valve in patients at extreme or high surgical risk.

**PRIMARY / SECONDARY ENDPOINTS**

- **Primary Safety**: Composite of all-cause mortality, stroke, life-threatening and major bleeding events, acute kidney injury (stage 2/3) and major vascular complications at 30 days.
- **Primary Effectiveness**: Composite of all-cause mortality, disabling stroke, and moderate or greater paravalvular leak (core lab assessment) at 1 year.
- **Secondary**: Moderate or greater PVL (core lab assessment) at 1 year.

**INDEPENDENT DATA ASSESSMENTS**

- Clinical Events Committee
- Core Labs (Angiography & CT/X-ray, Echocardiography, ECG, Pathology)
- Independent Data Validation (primary, secondary & clinical endpoints)
REPRISE III Study Organization

PRINCIPAL INVESTIGATORS
Ted E. Feldman, MD, Evanston Hospital, Cardiology Division, Evanston, IL, USA
Michael J. Reardon, MD, Houston Methodist DeBakey Heart & Vascular Center, Houston, TX, USA

CORE LABORATORIES
Angiography & CT/X-ray
Jeffrey J. Popma, MD (Director), Harvard Medical Faculty Physicians at Beth Israel Deaconess Medical Center, Boston, MA, USA

Echocardiography
Neil J. Weissman, MD (Director), MedStar Health Research Institute, Washington, DC, USA

Electrocardiography
Peter J. Zimetbaum, MD (Director), Baim Institute, Boston, MA, USA

Pathology
Renu Virmani, MD (Director), CV Path Institute, Inc., Gaithersburg, MD, USA

INDEPENDENT STUDY STATISTICIANS
Timothy Collier, MSc
Department of Medical Statistics, London School of Hygiene & Tropical Medicine, London, UK

John Gregson, PhD

DATA MONITORING COMMITTEE
Stuart Pocock, PhD; Chair
Department of Medical Statistics, London School of Hygiene & Tropical Medicine, London, UK

David Faxon, MD
Brigham & Women’s Hospital, Cardiovascular Division, Boston, MA, USA

Bernard Gersh, MB, ChB, DPhil
Mayo Clinic, Division of Cardiovascular Disease, Minneapolis, MN, USA

Steven Livesey, MD
Department of Cardiothoracic Surgery, Southampton General Hospital, Southampton, UK

CLINICAL EVENTS COMMITTEE
Sergio Waxman, MD (IC); Chair
Lahey Clinic, Burlington, MA

Gregory Smaroff, MD (CT Surg)

Carey Kimmelstiel, MD (IC)
Tufts New England Medical Center, Boston, MA, USA

Roberto Rodriguez, MD (CT Surg)
Lankenau Hospital, Wynnewood, PA, USA

Viken Babikian, MD (Neurology)
Boston Medical Center, Boston, MA, USA
REPRISE III Key Enrollment Criteria

**Inclusion**
- Symptomatic calcified native aortic stenosis
- NYHA Class ≥II; aortic annulus 20-27mm diameter
- STS score ≥8% and/or extreme or high surgical risk due to other specific criteria

**Exclusion – Clinical**
- AMI within 30 days
- Cerebrovascular accident or transient ischaemic attack within 6 months
- End-stage renal disease or GFR < 20 (based on Cockcroft-Gault formula)
- Cardiogenic shock or haemodynamic instability
- Any therapeutic invasive cardiac procedure within 30 days (except balloon aortic valvuloplasty or permanent pacemaker implantation)
- Untreated coronary artery disease requiring revascularisation
- GI bleed within 3 months
- Life expectancy <12 months due to non-cardiac, co-morbid conditions

**Exclusion – Anatomic**
- Unicuspid/bicuspid aortic valve, prosthetic valve or ring
- 4+ aortic, mitral, or tricuspid regurgitation
- Femoral arterial access that is not acceptable for both test & control devices
REPRISE III RCT Study Algorithm

Severe aortic stenosis; extreme or high operative risk
Annulus ≥20 mm and ≤27 mm; transfemoral access

Heart Team assessment \[\rightarrow\] Case Review Committee confirmation

Randomised 2:1 (Lotus : CoreValve)
N=912

Neurologist examination‡ \[\rightarrow\]

CoreValve† (26, 29 & 31mm)

Lotus Valve* (23, 25 & 27mm)

\[\downarrow\] Neurologist examination‡

- DAPT ≥1m OR warfarin + ASA or clopidogrel ≥1m (if anticoagulation needed)
- Clinical & echocardiographic follow-up: discharge or 7d, 30d, 6m, annually 1-5y

‡ Performed by a neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner
† CoreValve platform (includes CoreValve Classic and Evolut R)
* Centres with no Lotus experience enrolled 2 roll-in patients before commencing enrollment of the evaluable cohort

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## Enrollment

**912 patients between Sept 2014 & Dec 2015 at 55 centres**

### Top 20

<table>
<thead>
<tr>
<th>Enrollment</th>
<th>Patients</th>
<th>Enrollment</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vivek Rajagopal</td>
<td>74</td>
<td>Gregory Mishkel</td>
<td>25</td>
</tr>
<tr>
<td>Piedmont Heart Institute, Atlanta, GA, USA</td>
<td></td>
<td>St. John’s Hospital, Springfield, IL, USA</td>
<td></td>
</tr>
<tr>
<td>Raj Makkar</td>
<td>66</td>
<td>David Rizik</td>
<td>22</td>
</tr>
<tr>
<td>Cedars - Sinai Heart Institute, Los Angeles, CA, USA</td>
<td></td>
<td>Scottsdale-Lincoln Health Network, Scottsdale, AZ, USA</td>
<td></td>
</tr>
<tr>
<td>Tanvir Bajwa</td>
<td>58</td>
<td>Vijay Iyer</td>
<td>20</td>
</tr>
<tr>
<td>Aurora St. Luke’s Medical Center, Milwaukee, WI, USA</td>
<td></td>
<td>University at Buffalo/Gates Vascular Institute, Buffalo, NY, USA</td>
<td></td>
</tr>
<tr>
<td>Neal Kleiman</td>
<td>54</td>
<td>Thomas Gleason</td>
<td>20</td>
</tr>
<tr>
<td>Houston Methodist DeBakey Heart Center, Houston, TX, USA</td>
<td></td>
<td>University of Pittsburgh Medical Center, Pittsburgh, PA, USA</td>
<td></td>
</tr>
<tr>
<td>Axel Linke</td>
<td>49</td>
<td>Didier Tchéché</td>
<td>19</td>
</tr>
<tr>
<td>Herzzentrum Universität Leipzig, Leipzig, Germany</td>
<td></td>
<td>Clinique Pasteur, Toulouse, France</td>
<td></td>
</tr>
<tr>
<td>Dean Kereiakes</td>
<td>43</td>
<td>Joshua Rovin</td>
<td>19</td>
</tr>
<tr>
<td>The Christ Hospital Heart &amp; Vascular Center, Cincinnati, OH, USA</td>
<td></td>
<td>Morton Plant Mease Healthcare System, Clearwater, FL, USA</td>
<td></td>
</tr>
<tr>
<td>Ted Feldman</td>
<td>38</td>
<td>John Giacomini</td>
<td>19</td>
</tr>
<tr>
<td>Evanston Hospital Cardiology Division, Evanston, IL, USA</td>
<td></td>
<td>Veteran’s Administration Palo Alto Medical Cntr, Palo Alto, CA, USA</td>
<td></td>
</tr>
<tr>
<td>Ron Waksman</td>
<td>33</td>
<td>Robert Gooley</td>
<td>17</td>
</tr>
<tr>
<td>Washington Hospital Center, Washington, D.C., USA</td>
<td></td>
<td>Monash Medical Centre, Clayton, Victoria, Australia</td>
<td></td>
</tr>
<tr>
<td>Vinod Thourani</td>
<td>27</td>
<td>Didier Carrié</td>
<td>17</td>
</tr>
<tr>
<td>Emory University Hospital, Atlanta, GA, USA</td>
<td></td>
<td>Centre Hôpital Universitaire Rangueil, Toulouse, France</td>
<td></td>
</tr>
<tr>
<td>Robert Stoler</td>
<td>26</td>
<td>Robert Bersin</td>
<td>17</td>
</tr>
<tr>
<td>Baylor Heart &amp; Vascular Hospital, Dallas, TX, USA</td>
<td></td>
<td>Swedish Medical Center, Seattle, WA, USA</td>
<td></td>
</tr>
</tbody>
</table>

* United States (792), Germany (53), France (36), Australia (23), The Netherlands (6) & Canada (2)

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Patient Flow

55 Centres: United States, Germany, France, Australia, The Netherlands, Canada

Intent-to-Treat Analysis Set (N=912)

CoreValve (N=305)

1-Year f/u or VARC event
97.4% (297/305)

No assigned study valve: 8
4 withdrew consent preprocedure
4 with index procedure not completed

Implanted Analysis Set*
1-Year f/u or VARC event
98.0% (291/297)

Lotus Valve (N=607)

1-Year f/u or VARC event
96.7% (587/607)

No assigned study valve: 30
2 preprocedure deaths, 6 commercial,
9 withdrew consent, 10 crossover,
3 with index procedure not completed

Implanted Analysis Set
1-Year f/u or VARC event
98.1% (566/577)

*153 CoreValve Classic, 144 CoreValve Evolut R

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## Baseline Characteristics

### Demographics & Comorbidities – Intent-to-Treat

<table>
<thead>
<tr>
<th></th>
<th>CoreValve (N=305)</th>
<th>Lotus (N=607)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>82.9±7.6 (305)</td>
<td>82.8±7.1 (607)</td>
<td>0.71</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>52.1 (159)</td>
<td>50.1 (304)</td>
<td>0.56</td>
</tr>
<tr>
<td>STS score, %</td>
<td>6.9±4.1 (305)</td>
<td>6.7±4.0 (607)</td>
<td>0.49</td>
</tr>
<tr>
<td>euroSCORE 2011, %</td>
<td>6.4±5.5 (304)</td>
<td>6.4±5.5 (605)</td>
<td>1.00</td>
</tr>
<tr>
<td>Extreme surgical risk, %</td>
<td>21.6 (66)</td>
<td>23.1 (140)</td>
<td>0.63</td>
</tr>
<tr>
<td>Diabetes, treated, %</td>
<td>32.6 (99)</td>
<td>30.9 (187)</td>
<td>0.60</td>
</tr>
<tr>
<td>CAD, %</td>
<td>73.4 (224)</td>
<td>71.5 (433)</td>
<td>0.53</td>
</tr>
<tr>
<td>Prior PCI/CABG, %</td>
<td>43.9 (134)</td>
<td>44.6 (271)</td>
<td>0.84</td>
</tr>
<tr>
<td>Prior MI, %</td>
<td>19.0 (58)</td>
<td>18.3 (109)</td>
<td>0.78</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>31.6 (96)</td>
<td>35.1 (213)</td>
<td>0.28</td>
</tr>
<tr>
<td>Pacemaker, %</td>
<td>19.0 (58)</td>
<td>17.8 (108)</td>
<td>0.65</td>
</tr>
<tr>
<td>Prior stroke, %</td>
<td>14.5 (44)</td>
<td>11.3 (68)</td>
<td>0.17</td>
</tr>
<tr>
<td>PVD, %</td>
<td>25.7 (78)</td>
<td>31.1 (187)</td>
<td>0.09</td>
</tr>
<tr>
<td>COPD, %</td>
<td>30.7 (93)</td>
<td>31.9 (191)</td>
<td>0.72</td>
</tr>
</tbody>
</table>

Values are % (n) or mean±SD (n)

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### Baseline Characteristics

**Additional Risk Assessments – Intent-to-Treat**

<table>
<thead>
<tr>
<th>Qualifying Risk Criterion</th>
<th>CoreValve (N=305)</th>
<th>Lotus (N=607)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>STS Score ≥ 8, %</td>
<td>29.5 (90)</td>
<td>31.0 (188)</td>
<td>0.65</td>
</tr>
<tr>
<td>STS Score &lt; 8, %</td>
<td>70.5 (215)</td>
<td>69.0 (419)</td>
<td>0.65</td>
</tr>
<tr>
<td>CABG – reoperation risk, %</td>
<td>20.0 (43)</td>
<td>16.0 (67)</td>
<td>0.21</td>
</tr>
<tr>
<td>Severe lung disease, %</td>
<td>14.0 (30)</td>
<td>15.3 (64)</td>
<td>0.66</td>
</tr>
<tr>
<td>Orthopaedic disease, %</td>
<td>12.6 (27)</td>
<td>18.6 (78)</td>
<td>0.05</td>
</tr>
<tr>
<td>Age ≥ 90 years, %</td>
<td>12.6 (27)</td>
<td>10.0 (42)</td>
<td>0.33</td>
</tr>
<tr>
<td>Severe pulmonary hypertension, %</td>
<td>8.4 (18)</td>
<td>8.1 (34)</td>
<td>0.91</td>
</tr>
<tr>
<td>Hostile chest, %</td>
<td>4.7 (10)</td>
<td>4.1 (17)</td>
<td>0.73</td>
</tr>
<tr>
<td>Prior chest radiation therapy, %</td>
<td>3.7 (8)</td>
<td>4.1 (17)</td>
<td>0.84</td>
</tr>
<tr>
<td>Porcelain aorta, %</td>
<td>3.3 (7)</td>
<td>4.5 (19)</td>
<td>0.44</td>
</tr>
<tr>
<td>Neuromuscular disease, %</td>
<td>2.3 (5)</td>
<td>1.4 (6)</td>
<td>0.52</td>
</tr>
<tr>
<td>Frailty*, %</td>
<td>70.7 (152)</td>
<td>72.6 (304)</td>
<td>0.62</td>
</tr>
</tbody>
</table>

* Has at least one of the following: 5-metre walk >6 sec, Katz score of 3/6 or less, BMI <21, wheelchair bound, cannot live independently.
Baseline Echocardiography

Core Lab Data – Intent-to-Treat

<table>
<thead>
<tr>
<th></th>
<th>CoreValve (N=305)</th>
<th>Lotus (N=607)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic valve area (cm²)</td>
<td>0.70±0.19 (280)</td>
<td>0.69±0.19 (541)</td>
<td>0.33</td>
</tr>
<tr>
<td>Aortic regurgitation (mod/sev), %</td>
<td>8.0 (23/289)</td>
<td>6.5 (36/558)</td>
<td>0.41</td>
</tr>
<tr>
<td>Mean aortic gradient (mmHg)</td>
<td>43.9±12.3 (294)</td>
<td>44.6±13.4 (575)</td>
<td>0.40</td>
</tr>
<tr>
<td>Peak aortic gradient (mmHg)</td>
<td>72.4±18.1 (294)</td>
<td>73.6±20.8 (575)</td>
<td>0.40</td>
</tr>
<tr>
<td>Mitral regurgitation (mod/sev), %</td>
<td>11.7 (33/283)</td>
<td>10.7 (59/554)</td>
<td>0.66</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>55.9±11.8 (254)</td>
<td>56.1±11.4 (485)</td>
<td>0.80</td>
</tr>
<tr>
<td>Doppler velocity index</td>
<td>0.23±0.05 (292)</td>
<td>0.22±0.05 (553)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

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Values are % (n/N) or mean±SD (n)
Primary Composite Safety Endpoint*

Non-Inferiority Testing

*All-cause mortality, stroke, life-threatening/major bleed, stage 2/3 AKI, major vascular complications at 30 days

**Implanted‡**
- **Lotus:** 20.3% (117/576)
- **CoreValve:** 17.2% (51/297)

**Intent-to-Treat**
- **Lotus:** 19.0% (114/601)
- **CoreValve:** 16.2% (49/303)

**Non-inferiority criteria met for primary safety endpoint**

- **Lotus:** 20.3% (117/576)
- **CoreValve:** 17.2% (51/297)

**Non-inferiority P value = 0.003**

Upper 1-sided 97.5% CI†
- Difference: 3.1% ± 8.3%

**Lotus:** 19.0% (114/601)
- **CoreValve:** 16.2% (49/303)

**Non-inferiority P value = 0.001**

Upper 1-sided 97.5% CI†
- Difference: 2.8% ± 7.8%

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Primary Composite Safety Endpoint

1 Year – Intent-to-Treat

*All-cause mortality, stroke, life-threatening/major bleed, stage 2/3 AKI, major vascular complications

CoreValve vs Lotus

No. at risk

<table>
<thead>
<tr>
<th>Days</th>
<th>CoreValve</th>
<th>Lotus</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>305</td>
<td>607</td>
</tr>
<tr>
<td>30</td>
<td>253</td>
<td>485</td>
</tr>
<tr>
<td>90</td>
<td>233</td>
<td>456</td>
</tr>
<tr>
<td>180</td>
<td>215</td>
<td>438</td>
</tr>
<tr>
<td>270</td>
<td>207</td>
<td>419</td>
</tr>
<tr>
<td>365</td>
<td>165</td>
<td>334</td>
</tr>
</tbody>
</table>

P = 0.83

ITT; KM Event Rate ± 1.5 SE; log-rank P value

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Outcomes – 30 Days

**Intent-to-Treat**

<table>
<thead>
<tr>
<th>Primary Composite Safety Endpoint</th>
<th>CoreValve (N=305)</th>
<th>Lotus (N=607)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality, %</td>
<td>2.3 (7)</td>
<td>2.5 (15)</td>
<td>0.86</td>
</tr>
<tr>
<td>Stroke, %</td>
<td>4.3 (13)</td>
<td>4.8 (29)</td>
<td>0.72</td>
</tr>
<tr>
<td>Life threatening bleeding, %</td>
<td>5.0 (15)</td>
<td>8.0 (48)</td>
<td>0.09</td>
</tr>
<tr>
<td>Major bleeding, %</td>
<td>5.9 (18)</td>
<td>4.8 (29)</td>
<td>0.48</td>
</tr>
<tr>
<td>Major vascular complications, %</td>
<td>5.3 (16)</td>
<td>7.0 (42)</td>
<td>0.32</td>
</tr>
<tr>
<td>AKI (Stage 2/3 ≤7d), %</td>
<td>3.6 (11)</td>
<td>2.5 (15)</td>
<td>0.34</td>
</tr>
<tr>
<td>New pacemaker, %</td>
<td>15.8 (48)</td>
<td>29.1 (175)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>With no prior pacemaker, %</td>
<td>19.6 (48)</td>
<td>35.5 (175)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TAV-in-TAV deployment*, %</td>
<td>3.0 (9)</td>
<td>0.0 (0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Valve malpositioning*, %</td>
<td>2.6 (8)</td>
<td>0.0 (0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Procedural

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Non-inferiority criteria met for primary effectiveness endpoint

**Primary Effectiveness—Non-inferiority**

*Death, Disabling Stroke, ≥ Moderate PVL at 1 Year*

- **Implanted**:
  - **Lotus**: 16.4% (83/506)
  - **CoreValve**: 28.6% (74/259)

- **Intent-to-Treat**:
  - **Lotus**: 16.7% (87/520)
  - **CoreValve**: 29.0% (76/262)

**Difference**

- **Lotus**:
  - **Implanted**: -12.2%
  - **Intent-to-Treat**: -12.3%

**Upper 1-sided 97.5% CI†**

- **Lotus**:
  - **Implanted**: -6.3%
  - **Intent-to-Treat**: -6.4%

**Non-inferiority**

- **Lotus**:
  - **Implanted**: P value <0.001
  - **Intent-to-Treat**: P value <0.001

**Non-inferiority margin**

- 9.5% prespecified non-inferiority margin

---

† Upper 1-sided CI and P value are derived from the Farrington-Manning test

‡ Primary analysis set - enrolled patients implanted with the assigned valve

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Moderate or greater PVL is based on core lab assessment

SH-472806-AA_MAY2017
Primary Effectiveness – Superiority

Death, Disabling Stroke, ≥ Moderate PVL at 1 Year

Intent-to-Treat ‡
Lotus: 16.7% (87/520)
CoreValve: 29.0% (76/262)

Implanted
Lotus: 16.4% (83/506)
CoreValve: 28.6% (74/259)

Difference
Lotus: 16.4%
CoreValve: 28.6%
Difference: -12.2%

Upper 2-sided 95.0% CI†
-14 -12 -10 -8 -6 -4 -2 0 2 4 6 8 10
Favours Lotus
Favours CoreValve

Superiority achieved for primary effectiveness endpoint

† Superiority P value and 95% CI are derived from the Chi-square test
‡ Primary analysis set
### Primary Effectiveness Endpoint

**Components at 1 Year – Intent-to-Treat**

<table>
<thead>
<tr>
<th></th>
<th>CoreValve ($N=305$)</th>
<th>Lotus ($N=607$)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality*</td>
<td>13.5% (40/297)</td>
<td>11.9% (70/587)</td>
<td>0.51</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>9.8% (29/297)</td>
<td>7.7% (45/587)</td>
<td>0.29</td>
</tr>
<tr>
<td>Stroke†</td>
<td>9.4% (28/297)</td>
<td>7.0% (41/587)</td>
<td>0.20</td>
</tr>
<tr>
<td>Disabling*</td>
<td>7.1% (21/297)</td>
<td>3.6% (21/587)</td>
<td>0.02</td>
</tr>
<tr>
<td>Moderate or greater PVL*</td>
<td>11.1% (24/216)</td>
<td>2.0% (9/451)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Component of the primary effectiveness endpoint

† All patients had a neurological examination conducted by a neurology professional at baseline, discharge, 1 year, and after any suspected stroke. All patients also had NIHSS at discharge and 1 year and mRS at baseline and all f/u time points.
All-cause Mortality
1 Year – Intent-to-Treat

HR 0.87 [0.59, 1.28]
P=0.48

CoreValve
Lotus

No. at risk
CoreValve
Lotus

0 30 90 180 270 365
305 302 292 281 266 238
607 596 581 560 541 481

All-cause Mortality (%)
All-Cause Mortality/Disabling Stroke

1 Year – Intent-to-Treat

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HR 0.72 [0.51, 1.02]  
$P=0.06$

17.9%  
13.2%

CoreValve
Lotus

No. at risk
0 30 90 180 270 365
CoreValve 305 299 284 269 253 226
Lotus 607 591 572 550 534 474

Days

All-cause Mortality or Disabling Stroke (%)
Disabling Stroke
1 Year – Intent-to-Treat

HR 0.49 [0.27, 0.90]
P = 0.02

CoreValve
Lotus

Disabling Stroke (%)

No. at risk
CoreValve
Lotus

0 30 90 180 270 365
305 297 280 265 252 222
607 588 565 545 529 469

7.3%
3.6%
## Additional VARC Events at 1 Year

### Intent-to-Treat

<table>
<thead>
<tr>
<th>Event</th>
<th>CoreValve (N=305)</th>
<th>Lotus (N=607)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction, %</td>
<td>4.4 (13)</td>
<td>3.2 (19)</td>
<td>0.39</td>
</tr>
<tr>
<td>Life threatening bleeding, %</td>
<td>9.8 (29)</td>
<td>9.9 (58)</td>
<td>0.96</td>
</tr>
<tr>
<td>Major bleeding, %</td>
<td>8.4 (25)</td>
<td>8.3 (49)</td>
<td>0.97</td>
</tr>
<tr>
<td>New onset atrial fibrillation, %</td>
<td>4.7 (14)</td>
<td>6.6 (39)</td>
<td>0.25</td>
</tr>
<tr>
<td>Hospitalisation*, %</td>
<td>13.8 (41)</td>
<td>11.2 (66)</td>
<td>0.27</td>
</tr>
<tr>
<td>Endocarditis, %</td>
<td>0.0 (0)</td>
<td>0.7 (4)</td>
<td>0.31</td>
</tr>
<tr>
<td>Valve thrombosis, %</td>
<td>0.0 (0)</td>
<td>1.5 (9)</td>
<td>0.03</td>
</tr>
<tr>
<td>Repeat procedure†, %</td>
<td>2.0 (6)</td>
<td>0.2 (1)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

*Hospitalisation for valve-related symptoms or worsening congestive heart failure (NYHA class III or IV)
†Repeat procedure for valve-related dysfunction

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Values are % (n); binary event rates
Paravalvular Leak at 1 Year

Core Lab Assessment – Intent-to-Treat

**≥ Moderate PVL**

Superiority Testing

\[ P \leq 0.001 \]

<table>
<thead>
<tr>
<th></th>
<th>CoreValve (N=216)</th>
<th>Lotus (N=451)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ Moderate PVL</td>
<td>11.1%</td>
<td>2.0%</td>
</tr>
</tbody>
</table>

**All PVL**

<table>
<thead>
<tr>
<th></th>
<th>CoreValve (N=203)†</th>
<th>Lotus (N=442)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ Moderate</td>
<td>1.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Moderate</td>
<td>10.8</td>
<td>10.4</td>
</tr>
<tr>
<td>Mild</td>
<td>36.9</td>
<td>5.9</td>
</tr>
<tr>
<td>Trace</td>
<td>11.3</td>
<td></td>
</tr>
<tr>
<td>Trace</td>
<td>39.9</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>81.7</td>
<td></td>
</tr>
</tbody>
</table>

**Paravalvular Leak**

- Mod-Sev
- Moderate
- Mild
- Trace
- None

Superiority achieved for secondary endpoint

* There were no cases of severe PVL (grading per Pibarot, et al., JACC Cardiovasc Imaging 2015;8:340)

† For superiority testing, echocardiograms with less than moderate total aortic regurgitation and visible PVL that was not gradable were included in the group with less than moderate PVL. For reporting of all PVL, only echocardiograms with gradable PVL were included.

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Haemodynamics

Core Lab Data

<table>
<thead>
<tr>
<th></th>
<th>CoreValve (N)</th>
<th>Lotus (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Mean Aortic Gradient (mmHg)</td>
<td>294 (575)</td>
<td>281 (564)</td>
</tr>
<tr>
<td>30 Days Mean Aortic Gradient (mmHg)</td>
<td>261 (543)</td>
<td>280 (541)</td>
</tr>
<tr>
<td>6 Months Mean Aortic Gradient (mmHg)</td>
<td>233 (484)</td>
<td>247 (510)</td>
</tr>
<tr>
<td>1 Year Mean Aortic Gradient (mmHg)</td>
<td>219 (461)</td>
<td>238 (505)</td>
</tr>
<tr>
<td>Discharge Mean Aortic Gradient (mmHg)</td>
<td>281 (564)</td>
<td>247 (510)</td>
</tr>
<tr>
<td>30 Days Effective Orifice Area (cm²)</td>
<td>261 (543)</td>
<td>238 (505)</td>
</tr>
<tr>
<td>6 Months Effective Orifice Area (cm²)</td>
<td>233 (484)</td>
<td>209 (439)</td>
</tr>
<tr>
<td>1 Year Effective Orifice Area (cm²)</td>
<td>219 (461)</td>
<td>199 (419)</td>
</tr>
</tbody>
</table>

Lotus vs CoreValve: P <0.001 at discharge and later time points

Values are mean±SD; intent-to-treat analysis set

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Summary

In this large global randomised trial comparing Lotus to CoreValve the Lotus Valve demonstrated:

• Noninferiority for the 30-day primary safety endpoint†
  † All-cause mortality, stroke, life-threatening/major bleeding, stage 2/3 AKI and major vascular complications

• Superiority for the 1-year primary effectiveness endpoint‡
  ‡ All-cause mortality, disabling stroke and moderate or greater PVL

• Less moderate or greater paravalvular leak

• Fewer disabling strokes

• Fewer repeat procedures

• More valve thrombosis

• More new pacemaker implantations

• Less TAV-in-TAV deployment and less valve malpositioning