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
John Gregson, PhD
Department of Medical Statistics, London School of Hygiene & Tropical Medicine, London, UK

DATA MONITORING COMMITTEE
Stuart Pocock, PhD; Chair
David Faxon, MD
Bernard Gersh, MB, ChB, DPhil
Steven Livesey, MD
Department of Medical Statistics, London School of Hygiene & Tropical Medicine, London, UK
Brigham & Women’s Hospital, Cardiovascular Division, Boston, MA, USA
Mayo Clinic, Division of Cardiovascular Disease, Minneapolis, MN, USA
Department of Cardiothoracic Surgery, Southampton General Hospital, Southampton, UK

CLINICAL EVENTS COMMITTEE
Sergio Waxman, MD (IC); Chair
Gregory Smaroff, MD (CT Surg)
Carey Kimmelstiel, MD (IC)
Roberto Rodriguez, MD (CT Surg)
Viken Babikian, MD (Neurology)
Lahey Clinic, Burlington, MA
Tufts New England Medical Center, Boston, MA, USA
Lankenau Hospital, Wynnewood, PA, USA
Boston Medical Center, Boston, MA, USA

Caution: The Lotus aortic valve system is an Investigational Device restricted under federal law to investigational use only. Lotus™ is not available for sale in the U.S.
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
- LVEF <20%
REPRISE III RCT Study Algorithm

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

Heart Team assessment → Case Review Committee confirmation

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

Neurologist examination‡ →

CoreValve‡ (26, 29 & 31mm)
Lotus Valve* (23, 25 & 27mm)

• 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

Caution: The Lotus aortic valve system is an Investigational Device restricted under federal law to investigational use only. Lotus™ is not available for sale in the U.S.
## Enrollment

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

<table>
<thead>
<tr>
<th>Top 20</th>
<th>Patients</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vivek Rajagopal</td>
<td>74</td>
<td>Gregory Mishkel</td>
</tr>
<tr>
<td>Piedmont Heart Institute, Atlanta, GA, USA</td>
<td></td>
<td>St. John’s Hospital, Springfield, IL, USA</td>
</tr>
<tr>
<td>Raj Makkar</td>
<td>66</td>
<td>David Rizik</td>
</tr>
<tr>
<td>Cedars - Sinai Heart Institute, Los Angeles, CA, USA</td>
<td></td>
<td>Scottsdale-Lincoln Health Network, Scottsdale, AZ, USA</td>
</tr>
<tr>
<td>Tanvir Bajwa</td>
<td>58</td>
<td>Vijay Iyer</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>
</tr>
<tr>
<td>Neal Kleiman</td>
<td>54</td>
<td>Thomas Gleason</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>
</tr>
<tr>
<td>Axel Linke</td>
<td>49</td>
<td>Didier Tchétché</td>
</tr>
<tr>
<td>Herzzentrum Universitätsklinik Leipzig, Leipzig, Germany</td>
<td></td>
<td>Clinique Pasteur, Toulouse, France</td>
</tr>
<tr>
<td>Dean Kereiakes</td>
<td>43</td>
<td>Joshua Rovin</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>
</tr>
<tr>
<td>Ted Feldman</td>
<td>38</td>
<td>John Giacomini</td>
</tr>
<tr>
<td>Evanston Hospital Cardiology Division, Evanston, IL, USA</td>
<td></td>
<td>Veteran’s Administration Palo Alto Medical Ctr, Palo Alto, CA, USA</td>
</tr>
<tr>
<td>Ron Waksman</td>
<td>33</td>
<td>Robert Gooley</td>
</tr>
<tr>
<td>Washington Hospital Center, Washington, D.C., USA</td>
<td></td>
<td>Monash Medical Centre, Clayton, Victoria, Australia</td>
</tr>
<tr>
<td>Vinod Thourani</td>
<td>27</td>
<td>Didier Carrié</td>
</tr>
<tr>
<td>Emory University Hospital, Atlanta, GA, USA</td>
<td></td>
<td>Centre Hôpital Universitaire Rangueil, Toulouse, France</td>
</tr>
<tr>
<td>Robert Stoler</td>
<td>26</td>
<td>Robert Bersin</td>
</tr>
<tr>
<td>Baylor Heart &amp; Vascular Hospital, Dallas, TX, USA</td>
<td></td>
<td>Swedish Medical Center, Seattle, WA, USA</td>
</tr>
</tbody>
</table>

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

Caution: The Lotus aortic valve system is an Investigational Device restricted under federal law to investigational use only. Lotus™ is not available for sale in the U.S.
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)

Lotus Valve (N=607)
1-Year f/u or VARC event 96.7% (587/607)

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)

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

*153 CoreValve Classic, 144 CoreValve Evolut R

Caution: The Lotus aortic valve system is an Investigational Device restricted under federal law to investigational use only. Lotus™ is not available for sale in the U.S.
## 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 II, %</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)

Caution: The Lotus aortic valve system is an Investigational Device restricted under federal law to investigational use only. Lotus™ is not available for sale in the U.S.
## 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>

Values are % (n)

* 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

Caution: The Lotus aortic valve system is an Investigational Device restricted under federal law to investigational use only. Lotus™ is not available for sale in the U.S.
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>8.3 (24/290)</td>
<td>6.4 (36/562)</td>
<td>0.64</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>

Values are % (n/N) or mean±SD (n)

Caution: The Lotus aortic valve system is an Investigational Device restricted under federal law to investigational use only. Lotus™ is not available for sale in the U.S.
Primary Composite Safety Endpoint*

Non-Inferiority Testing

\[ \text{Difference} \quad \text{Upper 1-sided 97.5\% CI}^{\dagger} \]

**Implanted\(^\dagger\)**

\begin{align*}
\text{Lotus:} & \quad 20.3\% \\
& \quad (117/576) \\
\text{CoreValve:} & \quad 17.2\% \\
& \quad (51/297)
\end{align*}

\[ 3.1\% \quad 8.3\% \]

Non-inferiority P value = 0.003

**Intent-to-Treat**

\begin{align*}
\text{Lotus:} & \quad 19.0\% \\
& \quad (114/601) \\
\text{CoreValve:} & \quad 16.2\% \\
& \quad (49/303)
\end{align*}

\[ 2.8\% \quad 7.8\% \]

Non-inferiority P value = 0.001

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

Non-inferiority criteria met for primary safety endpoint

\(^\dagger\) Upper 1-sided CI and P value are derived from the Farrington-Manning test

\(^\ddagger\) Primary analysis set - enrolled patients implanted with the assigned valve

Caution: The Lotus aortic valve system is an Investigational Device restricted under federal law to investigational use only. Lotus™ is not available for sale in the U.S.
**Primary Composite Safety Endpoint**

1 Year – Intent-to-Treat

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

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

Caution: The Lotus aortic valve system is an Investigational Device restricted under federal law to investigational use only. Lotus™ is not available for sale in the U.S.
Outcomes – 30 Days

**Intent-to-Treat**

<table>
<thead>
<tr>
<th>Outcome</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>Disabling, %</td>
<td>3.3 (10)</td>
<td>2.0 (12)</td>
<td>0.23</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>Aortic valve malpositioning*, %</td>
<td>2.6 (8)</td>
<td>0.0 (0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Procedural; includes valve migration, valve embolization & ectopic valve deployment to discharge/7 days

Values are % (n); binary event rates

Caution: The Lotus aortic valve system is an Investigational Device restricted under federal law to investigational use only. Lotus™ is not available for sale in the U.S.

EuroPCR 2017
Primary Effectiveness—Non-inferiority

Death, Disabling Stroke, ≥ Moderate PVL at 1 Year

Implanted‡
Lotus: 15.4% (78/506)
CoreValve: 25.5% (66/259)

Intent-to-Treat
Lotus: 15.8% (82/520)
CoreValve: 26.0% (68/262)

Difference
-10.1%  -10.2%

Upper 1-sided
97.5% CI†
-4.4%  -4.5%

Non-inferiority
P value <0.001

Non-inferiority criteria met for primary effectiveness endpoint

‡ Primary analysis set - enrolled patients implanted with the assigned valve
† Upper 1-sided CI and P value are derived from the Farrington-Manning test
Moderate or greater PVL is based on core lab assessment

Caution: The Lotus aortic valve system is an Investigational Device restricted under federal law to investigational use only. Lotus™ is not available for sale in the U.S.

EuroPCR 2017
Primary Effectiveness – Superiority

Death, Disabling Stroke, ≥ Moderate PVL at 1 Year

**Intent-to-Treat**
- **Lotus:** 15.8% (82/520)
- **CoreValve:** 26.0% (68/262)

**Implanted**
- **Lotus:** 15.4% (78/506)
- **CoreValve:** 25.5% (66/259)

**Difference**
- **Lotus:** -10.1%
- **CoreValve:** -10.2%

**Upper 2-sided 95.0% CI**
- **Lotus:** -4.0%
- **CoreValve:** -3.9%

**Superiority**
- **Lotus:** P value < 0.001
- **CoreValve:** P value < 0.001

**Superiority achieved for primary effectiveness endpoint**

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

Caution: The Lotus aortic valve system is an Investigational Device restricted under federal law to investigational use only. Lotus™ is not available for sale in the U.S.
### 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>6.9% (15/216)</td>
<td>0.9% (4/452)</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

13.7%
11.9%

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

Caution: The Lotus aortic valve system is an Investigational Device restricted under federal law to investigational use only. Lotus™ is not available for sale in the U.S.
All-Cause Mortality/Disabling Stroke

1 Year – Intent-to-Treat

HR 0.72 [0.51, 1.02]  
\( P=0.06 \)

CoreValve
Lotus

17.9%
13.2%

No. at risk
CoreValve
Lotus

0 30 90 180 270 365
305 299 284 269 253 226
607 591 572 550 534 474

All-cause Mortality or Disabling Stroke (%)

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

Caution: The Lotus aortic valve system is an Investigational Device restricted under federal law to investigational use only. Lotus™ is not available for sale in the U.S.
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

Days

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

Caution: The Lotus aortic valve system is an Investigational Device restricted under federal law to investigational use only. Lotus™ is not available for sale in the U.S.
# 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

Values are % (n); binary event rates

Caution: The Lotus aortic valve system is an Investigational Device restricted under federal law to investigational use only. Lotus™ is not available for sale in the U.S.
Paravalvular Leak at 1 Year

Core Lab Assessment – Intent-to-Treat

≥ Moderate PVL

Superiority Testing

\( P < 0.001 \)

Patients with Moderate or Greater PVL (%)

<table>
<thead>
<tr>
<th></th>
<th>CoreValve (N=216)</th>
<th>Lotus (N=452)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ Moderate PVL</td>
<td>6.9%</td>
<td>0.9%</td>
</tr>
</tbody>
</table>

All PVL

Percent of Gradable Echocardiograms

<table>
<thead>
<tr>
<th></th>
<th>CoreValve (N=204)†</th>
<th>Lotus (N=443)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ Moderate PVL</td>
<td>1.0</td>
<td>0.9</td>
</tr>
<tr>
<td>Mild</td>
<td>6.4</td>
<td>5.9</td>
</tr>
<tr>
<td>Moderate</td>
<td>41.7</td>
<td>11.5</td>
</tr>
<tr>
<td>Moderate-Severe</td>
<td>11.3</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>39.7</td>
<td>81.7</td>
</tr>
</tbody>
</table>

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.

Caution: The Lotus aortic valve system is an Investigational Device restricted under federal law to investigational use only. Lotus™ is not available for sale in the U.S.
Haemodynamics

Core Lab Data

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

<table>
<thead>
<tr>
<th>Time Point</th>
<th>Mean Aortic Gradient (mmHg)</th>
<th>Effective Orifice Area (cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>CoreValve: 294 ± 575</td>
<td>CoreValve: 280 ± 541</td>
</tr>
<tr>
<td></td>
<td>Lotus: 281 ± 564</td>
<td>Lotus: 247 ± 510</td>
</tr>
<tr>
<td>Discharge</td>
<td>CoreValve: 12.2 ± 5.2</td>
<td>CoreValve: 12.0 ± 3.4</td>
</tr>
<tr>
<td></td>
<td>Lotus: 8.2 ± 4.0</td>
<td>Lotus: 7.3 ± 3.4</td>
</tr>
<tr>
<td>30 Days</td>
<td>CoreValve: 1.96 ± 0.52</td>
<td>CoreValve: 1.59 ± 0.45</td>
</tr>
<tr>
<td></td>
<td>Lotus: 1.65 ± 0.47</td>
<td>Lotus: 1.45 ± 0.46</td>
</tr>
<tr>
<td>6 Months</td>
<td>CoreValve: 1.98 ± 0.51</td>
<td>CoreValve: 1.74 ± 0.55</td>
</tr>
<tr>
<td></td>
<td>Lotus: 1.59 ± 0.45</td>
<td>Lotus: 1.49 ± 0.45</td>
</tr>
<tr>
<td>1 Year</td>
<td>CoreValve: 1.74 ± 0.55</td>
<td>CoreValve: 1.69 ± 0.52</td>
</tr>
<tr>
<td></td>
<td>Lotus: 1.49 ± 0.45</td>
<td>Lotus: 1.49 ± 0.45</td>
</tr>
</tbody>
</table>

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

Caution: The Lotus aortic valve system is an Investigational Device restricted under federal law to investigational use only. Lotus™ is not available for sale in the U.S.
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

- Smaller valve areas and higher gradients

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