Two-Year Outcomes With the Fully Repositionable and Retrievable Lotus™ Transcatheter Aortic Replacement Valve in 120 High-Risk Surgical Patients With Severe Aortic Stenosis: Results From the REPRISE II CE-Mark Study

Ian T. Meredith AM
MBBS, PhD, FRACP, FCSANZ, FACC, FAPSIC
Monash HEART, Monash Health & Monash University
Melbourne, Australia

On behalf of the REPRISE II Investigators

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Potential Conflicts of Interest

Speaker’s name: Ian T. Meredith, AM

Consultant Fees/Honoraria/Speaker’s Bureau:
Boston Scientific (Significant)

All faculty disclosures are available on the CRF Events App and online at www.crf.org/tct
Lotus Valve System Design Goals

- Pre-attached to catheter delivery system
- Bovine pericardial valve in woven nitinol frame
- Central radiopaque positioning marker to guide placement
- Valve functions early in deployment: hemodynamic stability
- Valve is fully repositionable & retrievable throughout entire deployment process
- Adaptive seal to minimize PVL

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REPRISE II Study Design

Objective
Evaluate safety & performance of the Lotus Valve System for TAVR in symptomatic patients with severe calcific native aortic stenosis who are considered high risk for surgical valve replacement

Design
• Prospective, single-arm; multicenter trial
• Follow-up at discharge/7 days, 30 days, 3 & 6 months, 1 year & annually through 5 years

Patients
• Symptomatic calcified native aortic stenosis
• Age ≥70y; NYHA Class ≥II; aortic annulus 19-27mm
• STS score ≥8% and/or high surgical risk due to frailty or comorbidities

Primary Endpoint (Device Performance)
Mean aortic valve pressure gradient at 30 days (Compared with a performance goal of 18mmHg)

Primary Endpoint (Safety)
All-cause mortality at 30 days
Additional REPRISE II Endpoints

VARC-2 Metrics

Safety
- Cardiovascular mortality
- Stroke
- Life-threatening/disabling bleed
- Acute kidney injury (Stage 2/3)
- Coronary obstruction (periproc.)
- Major vascular complications
- Repeat procedure for valve dysfunction
- MI (periprocedural & spontaneous)
- Hospitalization for valve-related symptoms or CHF
- New permanent pacemaker
- New-onset atrial fibrillation
- Prosthetic valve endocarditis, thrombosis, migration, embolization
- Cardiac tamponade (periproc.)

Effectiveness
- NYHA Class
- 5-meter gait speed (1 year vs. baseline)
- Quality of Life assessments
- Neurological assessments (NIHSS/mRS)

Valve Performance/Echocardiography
- Successful access, delivery, deployment, delivery system retrieval
- Success repositioning, if needed
- Successful valve retrieval, if needed
- Correct valve positioning
- Effective orifice area
- Mean & peak aortic valve gradients
- Peak aortic velocity
- Aortic valve regurgitation grade
REPRISE II Study Flow

Intent-To-Treat (N=120)

Lotus Valve Implanted (n=120)

No Lotus Valve Implanted (n=0)

2-Year Clinical Follow-up Available or Clinical Event: 100.0% (120/120)
2-Year TTE Assessment: n=78

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## Baseline Characteristics

### REPRISE II (N=120)

**Comorbidities & Baseline Scores**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>84.4 ± 5.3 (120)</td>
</tr>
<tr>
<td>NYHA Class III or IV</td>
<td>75.8% (91)</td>
</tr>
<tr>
<td>Gender (Female)</td>
<td>56.7% (68)</td>
</tr>
<tr>
<td>NYHA Class III or IV</td>
<td>75.8% (91)</td>
</tr>
<tr>
<td>Diabetes, treated</td>
<td>22.5% (27)</td>
</tr>
<tr>
<td>STS Score (v 2.73; %)</td>
<td>7.1 ± 4.6 (120)</td>
</tr>
<tr>
<td>Prior Pacemaker</td>
<td>6.7% (8)</td>
</tr>
<tr>
<td>STS Plus Score (%)</td>
<td>11.8 ± 8.0 (120)</td>
</tr>
</tbody>
</table>

**Echocardiographic Measurements***

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVA (cm²)</td>
<td>0.7 ± 0.2 (97)</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>54.3 ± 10.7 (61)</td>
</tr>
<tr>
<td>MR (mod/severe)</td>
<td>11.6% (13)</td>
</tr>
<tr>
<td>Mean gradient (mmHg)</td>
<td>46.4 ± 15.0 (104)</td>
</tr>
<tr>
<td>AR (mod/severe)</td>
<td>15.2% (17)</td>
</tr>
<tr>
<td>Peak gradient (mmHg)</td>
<td>76.5 ± 23.6 (104)</td>
</tr>
</tbody>
</table>

**Frailty Indices**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 Meter gait speed (sec)</td>
<td>9.2 ± 6.7 (119)</td>
</tr>
<tr>
<td>Max grip strength average (kg)</td>
<td>20.1 ± 12.8 (120)</td>
</tr>
<tr>
<td>Katz Index</td>
<td>5.7 ± 0.9 (120)</td>
</tr>
<tr>
<td>Mini-Cognitive Assessment for Dementia</td>
<td>3.6 ± 1.4 (120)</td>
</tr>
</tbody>
</table>

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*M Meredith, et al. JACC 2014; 64:1339. *Independent Core Lab assessment

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Primary Device Performance Endpoint

**REPRISE II (N=120)**

Mean Aortic Valve Gradient at 30 Days (N=120) (As-Treated population)

- Performance Goal = 18.0mmHg*
- 11.5mmHg ± UCB (12.6mmHg) is significantly below the performance goal (P<0.001)‡

**Successful access, delivery, deployment and system retrieval**
- 100.0% (120/120)

**Successful valve repositioning, if attempted** (n=31)
- 100.0% (31/31)

**Successful valve retrieval, if attempted** (n=6)
- 100.0% (6/6)

Aortic valve malpositioning
- 0%

Valve migration
- 0%

Valve embolization
- 0%

Ectopic valve deployment
- 0%

TAV-in-TAV deployment
- 0%

* Based on an expected mean of ≤15mmHg (literature review) plus a test margin of 3mmHg
‡ Meredith, et al. JACC 2014; 64:1339.

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**REPRISE II Mean Aortic Gradient & EOA**

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Gradient P value*</th>
<th>EOA P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline to Dis.</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline to 30D</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dis. to 30D</td>
<td>0.093</td>
<td>0.440</td>
</tr>
<tr>
<td>Baseline to 1Y</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline to 2Y</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Repeated measures and random effects ANOVA

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## Safety: Death & Stroke to 2 Years

### REPRISE II (N=120)

<table>
<thead>
<tr>
<th>KM Rates</th>
<th>30 Days</th>
<th>1 Year</th>
<th>2 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death</td>
<td>4.2% (5)</td>
<td>10.9% (13)</td>
<td>16.9% (20)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>4.2% (5)</td>
<td>6.7% (8)</td>
<td>10.4% (12)</td>
</tr>
<tr>
<td>Disabling stroke†</td>
<td>1.7% (2)</td>
<td>3.5% (4)</td>
<td>3.5% (4)</td>
</tr>
<tr>
<td>Non-disabling stroke†</td>
<td>4.2% (5)</td>
<td>6.0% (7)</td>
<td>6.0% (7)</td>
</tr>
</tbody>
</table>

Kaplan-Meier rates
Deaths between 1 & 2 yrs: Non CV: peritonitis & septic shock (n=1), acute kidney injury (n=1), cancer (n=1),
CV Deaths: endocarditis and progressive heart failure (n=1), progressive heart failure (n=3).

†All patients were assessed by a neurologist before and after TAVR.

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## Pacemaker Implantation at 2 Years

### REPRISE II (N=120)

#### New Permanent Pacemaker (N=120)

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Events</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 days to 1 Year</td>
<td>38</td>
<td>32.2%</td>
</tr>
<tr>
<td>1 Year to 2 Years</td>
<td>2</td>
<td>2.0%</td>
</tr>
</tbody>
</table>

- **3rd degree AV block on day 432**: 1 event
- **Symptomatic bradycardia on day 673**: 1 event

**0 Days to 2 Years**: 40 (34.2%)

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*Kaplan-Meier rates*

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Additional VARC 2 Safety Endpoints

**REPRISE II (N=120)**

Kaplan-Meier rates. Individual values may not sum to cumulative values due to rounding.

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Paravalvular Aortic Regurgitation

REPRISE II (N=120)

No moderate or severe paravalvular aortic regurgitation at 2 years

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NYHA Class Changes Over Time

REPRISE II (N=120)

<table>
<thead>
<tr>
<th>Measurement</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline to Discharge</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline to 2 Years</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Discharge to 30 Days</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1 Year to 2 Years</td>
<td>0.713</td>
</tr>
</tbody>
</table>

P values calculated from paired Wilcoxon signed-rank test

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At 2 years in the main 120-patient cohort:

- Sustained and excellent valve hemodynamic results
- >87% of patients without any paravalvular regurgitation
- No moderate or severe PVL in any patient
- Significant and sustained improvement in NYHA class functional status
- Adverse event rates consistent with those reported for other transcatheter valves
LOTUS Clinical Program

**Feasibility (Acute Safety, High Risk)**
N=11; single arm; 23mm valve size
1º Endpoint: Device success (VARC) without MACCE

**CE Mark Study (Safety & Performance, High Risk)**
N=120; single arm; 23 & 27mm valve sizes
1º Endpts: 30-day mean pressure gradient & 30-day mortality

**Safety/Performance (High Risk)**
N=130; single arm
23 & 27mm valve sizes

**REPRISE II Extended Cohort**
N=250
1º Safety Endpt: 30-day mortality

**Post Market Study (Safety & Performance, All Comers)**
N=1000; single arm; 23, 25, & 27mm valve sizes
1º Safety Endpoint: Mortality at 30 days & 1 year

**FDA Approval (Safety & Effectiveness, High Risk & InOp)**
N=1032; Global RCT; Lotus (23, 25, & 27mm) vs. CoreValve (26, 29, & 31mm)
1º Safety Endpoint: 30-day mortality, stroke, LT/major bleed, AKIN stage 2/3 or major vascular complications
1º Effectiveness Endpoint: 1-year mortality, stroke, LT bleed, disabling stroke or mod/severe PVL

**REPRISE III Extension**
Enrolling Q3 2014

**REPRISE Japan**
Enrolling Q2 2015

**PMDA Approval (Safety & Effectiveness, High Risk & InOp)**
N=50; single arm; 23, 25, & 27mm valve sizes
1º Endpoint similar to REPRISE III; safety at 30d, effectiveness at 6 months

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