Two-year outcomes with a fully repositionable and retrievable percutaneous aortic valve in 250 high surgical risk patients: Results from the REPRISE II trial extended cohort

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MonashHeart, Clayton, Victoria, Australia

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on behalf of the REPRISE II Investigators
Disclosures

Ian T. Meredith AM

• Consultant Fee / Honoraria / Speaker’s Bureau:
  – Boston Scientific (Significant)

The REPRISE studies are sponsored and funded by Boston Scientific Corporation.
Lotus Valve System
Fully repositionable & retrievable

• Controlled mechanical expansion for precise placement
• Early valve function enables hemodynamic stability

Bovine Pericardium Leaflets
Braided Nitinol Frame
Radiopaque Positioning Marker
Adaptive Seal designed to minimise PVL
REPRISE II Study with Extended Cohort

OBJECTIVE

- Evaluate safety & performance of the Lotus Valve System for TAVI in symptomatic patients with severe calcific aortic stenosis considered high risk for surgical valve replacement

DESIGN

- Prospective; single-arm; multicentre
- Available valve sizes: 23mm & 27mm
- F/U at 7 days/discharge, 30 days, 3 & 6 months, annually 1–5 years

INDEPENDENT DATA ASSESSMENTS

- Clinical Events Committee
- Core Labs: Angiography, ECG, Echocardiography, Pathology
## REPRISE II Study Organisation

### PRINCIPAL INVESTIGATOR

Ian T. Meredith, MBBS, PhD, Monash Medical Centre, Clayton, Australia

### CORE LABORATORIES

<table>
<thead>
<tr>
<th>Discipline</th>
<th>Director</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiography &amp; CT/X-ray</td>
<td>Jeffrey J. Popma, MD (Director)</td>
<td>Harvard Medical Faculty Physicians at Beth Israel Deaconess Medical Center, Boston, MA, USA</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>Neil J. Weissman, MD (Director)</td>
<td>MedStar Health Research Institute, Washington, DC, USA</td>
</tr>
<tr>
<td>Electrocardiography</td>
<td>Peter J. Zimetbaum, MD (Director)</td>
<td>Harvard Clinical Research Institute, Boston, MA, USA</td>
</tr>
<tr>
<td>Pathology</td>
<td>Renu Virmani, MD (Director)</td>
<td>CV Path Institute, Inc., Gaithersburg, MD, USA</td>
</tr>
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### CLINICAL EVENTS COMMITTEE

<table>
<thead>
<tr>
<th>Chair</th>
<th>Co-Chair</th>
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<tbody>
<tr>
<td>Sergio Waxman, MD</td>
<td>Gregory Smaroff, MD (CT Surg)</td>
</tr>
<tr>
<td>Carey Kimmelstiel, MD</td>
<td>Roberto Rodriguez, MD (CT Surg)</td>
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<td></td>
<td>Viken Babikian, MD (Neurologist)</td>
</tr>
</tbody>
</table>
## Enrollment – REPRISE II with Extended Cohort

*250 patients between Oct 2012 & Apr 2014 at 20 sites*

<table>
<thead>
<tr>
<th>Patient Name</th>
<th>Site Details</th>
<th>Patients</th>
</tr>
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<tbody>
<tr>
<td>Ian Meredith</td>
<td>Monash Medical Centre, Clayton, Australia</td>
<td>38</td>
</tr>
<tr>
<td>Nicolas Dumonteil</td>
<td>Centre Hôpital Universitaire Rangueil, Toulouse, France</td>
<td>29</td>
</tr>
<tr>
<td>Daniel Blackman</td>
<td>The General Infirmary, Leeds, UK</td>
<td>22</td>
</tr>
<tr>
<td>Didier Tchétché</td>
<td>Clinique Pasteur, Toulouse, France</td>
<td>21</td>
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<tr>
<td>David Hildick-Smith</td>
<td>Royal Sussex County Hospital, Brighton, UK</td>
<td>19</td>
</tr>
<tr>
<td>Ganesh Manoharan</td>
<td>Royal Victoria Hospital, Belfast, UK</td>
<td>19</td>
</tr>
<tr>
<td>Darren Walters</td>
<td>The Prince Charles Hospital, Brisbane, Australia</td>
<td>19</td>
</tr>
<tr>
<td>Jan Harnek</td>
<td>University Hospital of Lund, Lund, Sweden</td>
<td>16</td>
</tr>
<tr>
<td>Stephen Worthley</td>
<td>Royal Adelaide Hospital, Adelaide, Australia</td>
<td>13</td>
</tr>
<tr>
<td>Gilles Rioufol</td>
<td>Hôpital Cardiologique de Lyon, Bron, France</td>
<td>10</td>
</tr>
<tr>
<td>Thierry Lefèvre</td>
<td>Institut Cardiovasculaire - Paris Sud, Massy, France</td>
<td>9</td>
</tr>
<tr>
<td>Thomas Modine</td>
<td>CHRU Lille - Hôpital Cardiologique, Lille, France</td>
<td>9</td>
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<tr>
<td>Nicolas Van Mieghem</td>
<td>Erasmus Medical Center, Rotterdam, The Netherlands</td>
<td>8</td>
</tr>
<tr>
<td>Rüdiger Lange</td>
<td>Deutsches Herzzentrum Muenchen, Muenchen, Germany</td>
<td>4</td>
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<tr>
<td>Robert Whitbourn</td>
<td>St. Vincent's Hospital (Melbourne), Fitzroy, Australia</td>
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<tr>
<td>Simon Redwood</td>
<td>Guys and St. Thomas’ NHS Foundation Trust, London, UK</td>
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<tr>
<td>Corrado Tamburino</td>
<td>Ospedale Ferrarotto, Catania, Italy</td>
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</tr>
<tr>
<td>Ralf Müller</td>
<td>HELIOS Klinikum Siegburg, Siegburg, Germany</td>
<td>2</td>
</tr>
<tr>
<td>Eulogio Garcia</td>
<td>Hospital Clinico San Carlos, Madrid, Spain</td>
<td>1</td>
</tr>
<tr>
<td>Stephan Windecker</td>
<td>Universitätsspital Bern, Bern, Switzerland</td>
<td>1</td>
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</tbody>
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REPRISE II Study with Extended Cohort

Preplanned Analysis of Pooled Data

- REPRISE II (N=120)
  - 1° Device Performance Endpoint (N=120)
    - 30-day mean aortic valve gradient compared to a performance goal of 18 mmHg*
      - As-Treated Population

- REPRISE II Extension (N=130)
  - 1° Safety Endpoint (N=250)
    - 30-day all-cause mortality compared to a performance goal of 16%†
      - Intent-to-Treat Population

Additional endpoints according to the VARC-2 metrics

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* Meredith, et al. JACC 2014;64:1339
† Meredith, et al. PCR London Valves 2014
Study Flow – REPRISE II with Extended Cohort

Intent-To-Treat
N=250

Lotus Valve Implanted at Index Procedure
N=248

Valve Implanted Later: n=1

As Treated Analysis Set
N=249

Withdrew Consent: n=2
Lost to F/U: n=1
Missed Visit: n=7

2-Year Follow-up Data Available or Clinical Event: 96.0% (239/249)

2-Year TTE Assessment: N=146

Intent-to-treat population.
## Baseline Characteristics

**REPRISE II with Extended Cohort (N=250; Intent-To-Treat)**

### Comorbidities & Baseline Scores

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>84.0 ± 5.2</td>
<td>250</td>
</tr>
<tr>
<td>Gender (Female)</td>
<td>52.4%</td>
<td>131</td>
</tr>
<tr>
<td>Diabetes, treated</td>
<td>24.0%</td>
<td>60</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>37.2%</td>
<td>93</td>
</tr>
<tr>
<td>NYHA Class III or IV</td>
<td>77.2%</td>
<td>193</td>
</tr>
<tr>
<td>euroSCORE 2011 (%)</td>
<td>6.4 ± 6.2</td>
<td>250</td>
</tr>
<tr>
<td>STS Score (v 2.73; %)</td>
<td>6.5 ± 4.2</td>
<td>250</td>
</tr>
<tr>
<td>STS Plus Score (%)</td>
<td>10.6 ± 7.7</td>
<td>250</td>
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### Echocardiographic Measurements*

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>Count</th>
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<tbody>
<tr>
<td>AVA (cm²)</td>
<td>0.7 ± 0.2</td>
<td>197</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>53.1 ± 10.5</td>
<td>126</td>
</tr>
<tr>
<td>MR (mod/severe)</td>
<td>10.6%</td>
<td>24</td>
</tr>
<tr>
<td>Mean gradient (mmHg)</td>
<td>45.2 ± 13.6</td>
<td>212</td>
</tr>
<tr>
<td>AR (mod/severe)</td>
<td>13.3%</td>
<td>29</td>
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<tr>
<td>Peak gradient (mmHg)</td>
<td>74.7 ± 21.1</td>
<td>212</td>
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</table>

### Frailty Indices

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>Count</th>
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<tbody>
<tr>
<td>5 Meter gait speed (sec)</td>
<td>8.6 ± 5.2</td>
<td>236</td>
</tr>
<tr>
<td>Max grip strength average (kg)</td>
<td>21.1 ± 11.5</td>
<td>246</td>
</tr>
<tr>
<td>Katz Index</td>
<td>5.7 ± 0.8</td>
<td>247</td>
</tr>
<tr>
<td>Mini-Cognitive Assessment for Dementia</td>
<td>3.5 ± 1.4</td>
<td>244</td>
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</tbody>
</table>

* Independent Core Lab assessment
Device Performance

REPRISE II with Extended Cohort (N=250; Intent-To-Treat)

Successful access, delivery, deployment & system retrieval 98.8%
Successful valve repositioning, if attempted (n=85) 100.0%
  Partial valve resheathing (n) 71
  Full valve resheathing (n) 14
Successful valve retrieval, if attempted (n=13) 92.3%
Aortic valve malpositioning 0.0%
  Valve migration 0.0%
  Valve embolisation 0.0%
  Ectopic valve deployment 0.0%
  TAV-in-TAV deployment 0.0%
Procedural Device Success – VARC 2 Metrics

REPRISE II with Extended Cohort (N=250; Intent-To-Treat)
Core-lab adjudicated

- No procedural mortality: 98.4% (246/250)
- Correct positioning of one valve in proper location: 99.2% (248/250)
- Mean aortic valve gradient <20 mmHg: 95.0% (210/221)
- Peak velocity <3 m/s: 94.6% (210/222)
- No moderate/severe prosthetic valve regurgitation: 98.2% (217/221)
Primary Endpoints

REPRISE II with Extended Cohort

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

Performance Goal = 18.0mmHg*

11.5mmHg

11.5mmHg ± UCB (12.6mmHg)
is significantly below the performance goal (P<0.001)‡

All-cause Mortality at 30 Days (N=250)
(Intent-to-Treat Population)

Performance Goal = 16%†

4.4%

4.4% ± UCB (6.97%)
is significantly below the performance goal (P<0.001)§

* Based on an expected mean of ≤15mmHg (literature review) plus a test margin of 3mmHg
† Based on an expected rate of 9.8% (literature review) plus a test margin of 6.2%
‡ Meredith, et al. JACC 2014; 64:1339.
Mean Aortic Gradient & EOA at 2 Years

REPRISE II With Extended Cohort (N=249; As Treated)

Values are mean ± standard deviations. As-treated population.
Paravalvular Aortic Regurgitation at 2 Years

REPRISE II With Extended Cohort (N=249; As Treated)

No moderate or severe paravalvular aortic regurgitation at 2 years

Core-lab adjudicated data. Values may not add to 100% due to rounding. As-treated population.
### Safety: Death & Stroke at 2 Years

**REPRISE II with Extended Cohort (N=249; As Treated)**

<table>
<thead>
<tr>
<th>Event</th>
<th>30 Days</th>
<th>1 Year</th>
<th>2 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death</td>
<td>4.0% (10)</td>
<td>11.8% (29)</td>
<td>19.1% (47)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>3.6% (9)</td>
<td>7.8% (19)</td>
<td>9.5% (23)</td>
</tr>
<tr>
<td>Disabling stroke</td>
<td>2.9% (7)</td>
<td>3.7% (9)</td>
<td>4.7% (11)</td>
</tr>
<tr>
<td>Non-disabling stroke</td>
<td>4.1% (10)</td>
<td>4.9% (12)</td>
<td>4.9% (12)</td>
</tr>
</tbody>
</table>

All REPRISE II patients (n=120) were assessed by a neurologist before and after TAVI. KM rates.
Pacemaker Implantation at 2 Years

**REPRISE II with Extended Cohort (N=249; As Treated)**

*New Permanent Pacemaker (N=249)*

0 days to 1 Year  
81 (33.1%)

1 Year to 2 Years  
4 (1.9%)

3rd degree AV block on day 432  
1

Symptomatic bradycardia (days 527, 663, and 673)  
3

0 Days to 2 Years  
85 (35.1%)

Kaplan-Meier rates. Events may not add over time due to censoring.
Additional VARC 2 Safety Endpoints at 2 Years

REPRISE II With Extended Cohort (N=249; As Treated)

Periprocedural (≤ 72 h)

2 Years

Percent of Patients (N=249)

- Coronary Obstruction
- MI <72 h
- Cardiac Tamponade
- MI >72 h
- Repeat Proc. Valve Dysfunct.
- Major Vascular Compl.
- Life-threat. Bleed
- AKI (Stage 2/3)
- Valve Thrombosis
- Valve Endocarditis

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

SH 441722 AA DEC 2016
NYHA Class Changes at 2 Years

**REPRISE II with Extended Cohort (N=249; As Treated)**

<table>
<thead>
<tr>
<th>Measurement</th>
<th>P value</th>
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</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>0.80</td>
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</table>

P values calculated from paired Wilcoxon signed-rank test.
Conclusions

REPRISE II with Extended Cohort (N=250)

• At 2 years
  – Continued excellent safety and efficacy
  – Conserved valve haemodynamics
  – No moderate or severe PVL
    ▪ >90% of patients had no/trace PVL
  – Significant and sustained improvement in NYHA functional class
    ▪ >92% of patients NYHA Class I or Class II
  – Adverse event rates consistent with those reported for other valves

• These findings are consistent with those reported for the REPRISE II main cohort at 2 years, and support the use of the Lotus Valve for the treatment of aortic stenosis in high-risk surgical patients.