Transcatheter Intracardiac Shunt Device Provides Sustained Clinical Benefit at One Year in Heart Failure with Preserved or Mildly Reduced Ejection Fraction: The REDUCE LAP Heart Failure Trial

David M Kaye MD, PhD
on behalf of the REDUCE LAP HF Investigators
Disclosures

DK is an unpaid member of the Corvia Medical, Inc. Scientific Advisory Group
Introduction

- Heart failure with preserved ejection fraction (HFPEF) has a complex pathophysiology and remains a therapeutic challenge.
- Elevated left atrial pressure, especially during exercise, is a near-universal finding in patients with HFPEF.

![Graph showing PCWP (mmHg) vs. Time (Baseline, Feet up, 1 Min, Peak Exercise) for Non HF and HFPEF groups.]

- Increased LV passive stiffness
- Reduced active LV relaxation
- Reduced LA compliance

Borlaug CircHF 2010
• The magnitude of the exercise-mediated rise in PCWP in HFPEF is related to both symptoms and outcome.

### SYMPTOMS

**Six minute walk (meters)**

- *Six minute work load corrected PCWP (mmHg/W/kg)*
  - $r = -0.47$
  - $p < 0.001$

### SURVIVAL

**Survival (%)**

- Work corrected PCWP $< 25.5$ mmHg/W/kg
  - $p = 0.03$
- Work corrected PCWP $> 25.5$ mmHg/W/kg

**Dorfs EHJ 2014**

REDUCE LAP-HF Unpublished data
Left Atrial Decompression: IASD Rationale

- Computer simulation demonstrated that an 8mm interatrial shunt device (IASD®) would provide acute LA decompression during exercise

![Graph showing pressure before and after shunt](image)

Kaye et al JCardFail 2014
InterAtrial Shunt Device - Mode of Action

Transcatheter interatrial shunt device

- Elevated LV filling pressures (Elevated LAP)
- Pulmonary Venous hypertension
- Pulmonary Congestion & Dyspnea (rest/exercise)

CAUTION  Investigational device. Limited by Federal (or United States) law to investigational use
Inclusion Criteria (n=64):
Open label
LVEF ≥ 40%,
NYHA class II-IV
Elevated PCWP
≥ 15 mmHg (rest) or
≥ 25 (supine bicycle exercise)

6 month outcomes

NYHA Class

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Baseline</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>Class II</td>
<td>40</td>
<td>30</td>
</tr>
<tr>
<td>Class III</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Class IV</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

p < 0.001

MLWHF

<table>
<thead>
<tr>
<th>Score</th>
<th>Baseline</th>
<th>Follow-up</th>
</tr>
</thead>
</table>

p < 0.001

6 MWT

<table>
<thead>
<tr>
<th>Metres</th>
<th>Baseline</th>
<th>Follow-up</th>
</tr>
</thead>
</table>

p = 0.003

Exercise time

<table>
<thead>
<tr>
<th>Minutes</th>
<th>Baseline</th>
<th>Follow-up</th>
</tr>
</thead>
</table>

p = 0.03

& reduced exercise PCWP

Objective & Methods

• To assess **device safety** (major adverse cardiac, cerebrovascular and systemic embolic events -MACCE), and **device performance** one year post implant.
  - device performance: shunting (echocardiography)

• To evaluate **persistence of clinical benefit**:
  - clinical efficacy: NYHA class, quality of life (MLWHFQ), 6MW distance
  - cardiac structure and function (echocardiography)
  - rest and exercise hemodynamics (**optional sub-study**, n=18)
    - oximetry to assess Qp:Qs (n=13)

• Study monitored by independent CEC and DSMB
## Baseline Characteristics (n=64)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Y)</td>
<td>69±8</td>
</tr>
<tr>
<td>Gender (% Female/Male)</td>
<td>66 / 34</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>47±7</td>
</tr>
<tr>
<td>NYHA Class (n, II/III/IV)</td>
<td>18/46/0</td>
</tr>
<tr>
<td>Minnesota Living with HF Score</td>
<td>49 ± 20</td>
</tr>
<tr>
<td>BMI kg/m²</td>
<td>33 ± 6</td>
</tr>
<tr>
<td>Permanent AF (%)</td>
<td>36</td>
</tr>
<tr>
<td>NT-Pro BNP (median, IQR pg./ml)</td>
<td>377 (222-925)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>81</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>33</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>36</td>
</tr>
<tr>
<td>Diuretics at baseline (%)</td>
<td>91</td>
</tr>
<tr>
<td>Resting CVP (mm Hg)</td>
<td>9 ± 4</td>
</tr>
<tr>
<td>Resting PCWP (mm Hg)</td>
<td>17 ± 5</td>
</tr>
</tbody>
</table>
Safety (MACCE) and Device Performance

### MACCE event

<table>
<thead>
<tr>
<th>MACCE event</th>
<th>Six months %</th>
<th>One year %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0</td>
<td>4.7 (3/64)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
<td>1.5 (1/64)* (pt died)</td>
</tr>
<tr>
<td>MI</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Systemic embolic event</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Implant removal</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

### Effectiveness

<table>
<thead>
<tr>
<th>Effectiveness</th>
<th>Six months %</th>
<th>One year %</th>
</tr>
</thead>
<tbody>
<tr>
<td>L→ R Shunt flow (Echo)</td>
<td>100 (49/49)</td>
<td>100 (48/48)</td>
</tr>
<tr>
<td>R→ L Shunt flow (Echo)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Qp:Qs</td>
<td>1.27 ± 0.24</td>
<td>1.28 ± 0.25</td>
</tr>
</tbody>
</table>

Device patency confirmed in 54 subjects (by echo or oximetry)
**Sustained Clinical Efficacy**

**Patients with data at all 3 time points.**

**NYHA Class**

- Baseline: 100%
- 6M: 90%
- 12M: 80%

**MLWHF Score**

- Baseline: Mean Δ at 1 year: 15 points
- 6M: Mean Δ at 1 year: 33m

**6MWD**

- Baseline: **
- 6M: **
- 12M: **

**p<0.01, ***p<0.001 vs baseline**
Echocardiographic Results

No change in atrial volumes

*p<0.05, **p<0.01, ***p<0.001
## Invasive Hemodynamic Results (rest)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Six months</th>
<th>One year</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA pressure</td>
<td>8 ± 3</td>
<td>11 ± 6</td>
<td>10 ± 4</td>
</tr>
<tr>
<td>PA_{mean} pressure</td>
<td>25 ± 8</td>
<td>23 ± 7</td>
<td>26 ± 8</td>
</tr>
<tr>
<td>Wedge pressure</td>
<td>19 ± 6</td>
<td>16 ± 8</td>
<td>17 ± 6</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>5.2 ± 1.3</td>
<td>6.3 ± 1.4**</td>
<td>6.7 ± 1.8**</td>
</tr>
</tbody>
</table>

Patients with data at all 3 time points.

** p<0.01 vs baseline
Exercise Hemodynamic Results

**Exercise time**

- Baseline: 6 minutes
- 6M: 7 minutes
- 12M: 10 minutes

**Workload**

- Baseline: 60 watts
- 6M: 50 watts
- 12M: 50 watts

**PCWP**

- Baseline: 25 mmHg
- 6M: 30 mmHg
- 12M: 30 mmHg

**Cardiac Output**

- Baseline: 10 L/min
- 6M: 12 L/min
- 12M: 15 L/min

* p<0.05, ** p<0.01 vs baseline
Exercise Hemodynamic Results-2

IASD therapy provides increased work capacity for a given LA pressure

* p<0.05, ** p<0.01 vs baseline
Summary and Conclusions

• Implantation of an interatrial shunt device appears to be safe with an acceptable MACCE rate through one year of follow-up.

• Interatrial shunt device patency was maintained through one year.

• The clinical and hemodynamic benefit observed 6 months after implant was sustained through one year, with no evidence of adverse sequelae
  • Meaningful improvements in NYHA class, exercise capacity and QOL
  • Clinically meaningful reduction in normalized PCWP

• Randomised trials are required and ongoing to determine the value of this novel strategy for the management of HFPEF.