Transcatheter InterAtrial Shunt Device for the Treatment of Heart Failure: Results From the REDUCE LAP-HF I Randomized Controlled Trial

Sanjiv J. Shah, MD, FAHA
On behalf of the REDUCE LAP-HF I investigators and research staff
Introduction

- HFpEF (LVEF > 50%) and HFmrEF (LVEF 40-50%):
  - Increasing in prevalence
  - High morbidity/mortality
  - No proven therapies
  - Heterogeneous syndromes
  - Common pathophysiologic thread: ↑LA pressure at rest or with exertion

Borlaug BA, et al. Circ Heart Fail 2010
Importance of ↑LA pressure in HFpEF

**EXERCISE CAPACITY**

Wolsk E...Gustafsson F. *EJHF* 2017

- **Six minute walk (meters)**
  - 600
  - 400
  - 200
  - 0

- **Workload corrected PCWP (mmHg/W/kg)**
  - 0
  - 100
  - 200
  - 300

- **r** = -0.47

- **p** < 0.001

**SURVIVAL**


- **Work-corrected PCWP**
  - < 25.5 mmHg/W/kg
  - > 25.5 mmHg/W/kg

- **P** = 0.03

Follow-up (years)

Survival (%)
InterAtrial Shunt Device

IASD proposed mode of action: dynamic decompression of overloaded LA chamber by shunting blood from LA $\rightarrow$ RA

Feldman T…Shah SJ. *Circ Heart Fail* 2016
InterAtrial Shunt Device

Simulation using exercise hemodynamic data from HFpEF patients

Kaye D…Burkhoff D. J Card Fail 2014
Results of IASD open-label study (n=64)

Inclusion criteria:

- Open label
- LVEF ≥ 40%
- NYHA class II-IV
- Elevated PCWP
  - ≥ 15 mmHg (rest) or
  - ≥ 25 mmHg (supine bicycle exercise)

Acceptable safety profile at 12 months

![Graphs showing changes in exercise time, workload, PCWP, and work indexed PCWP over baseline at 6M and 12M.]

*p<0.05, **p<0.01 vs. baseline

Hasenfuß G...Kaye D. Lancet 2016
Hypothesis

• At 1 month after randomization, compared to sham control, implantation of the IASD System II in patients with HF and EF $\geq 40\%$ will result in:
  - **Mechanistic effect:** Reduction in exercise PCWP
  - **Safety:** No increase in major adverse cardiovascular, cerebral, or renal events (MACCRE)
REDUCE LAP-HF I RCT: Study Design

• Phase 2, randomized, sham-controlled trial
• Patient- and HF physician-blinded
• 1:1 randomization to IASD vs. sham control
  ➢ Active treatment: Femoral venous access with ICE/TEE + transseptal IASD implantation
  ➢ Sham control: Femoral venous access with examination of interatrial septum and LA with ICE/TEE
• Independent DSMB, CEC, hemodynamic core lab
Primary and Secondary Outcomes

• Primary outcomes (1 month):
  ▶ Mechanistic effect: Reduction in exercise PCWP
  ▶ Safety: Major adverse cardiovascular, cerebral, or renal events (MACCRE)

• Secondary outcomes (1 month):
  ▶ Change in PCWP at peak exercise
  ▶ Change in exercise duration
  ▶ Change in PA pressures
Key inclusion/exclusion criteria

• Inclusion criteria:
  ➤ Symptomatic HF
  ➤ NYHA class III or ambulatory IV
  ➤ LVEF ≥ 40%
  ➤ HF hospitalization in prior 12 months or ↑BNP (or ↑NTproBNP)
  ➤ Echo evidence of LV diastolic dysfunction
  ➤ ↑Exercise PCWP (≥ 25 mmHg)
  ➤ ↑PCWP-RAP gradient (≥ 5 mmHg)

• Exclusion criteria:
  ➤ Stage D HF
  ➤ Cardiac index < 2.0 L/min/m²
  ➤ Prior history of LVEF < 30%
  ➤ Significant valve disease
    • ≥ 3+ MR, ≥ 2+ TR, ≥ 2+ AR
  ➤ Significant RV dysfunction
    • TAPSE < 1.4 cm, RV > LV size, or RVFAC < 35%
  ➤ RAP > 14 mmHg
  ➤ PVR > 4 Wood units
Statistical Analysis

• Power calculation:
  ➤ N=20 in each group to detect 6.0±7.2 mmHg greater reduction in exercise PCWP at 1 month in IASD group
  ➤ Two-sided $\alpha=0.05$ and power = 82%

• Primary outcome analysis:
  ➤ Mixed effects model repeated measures (MMRM) analysis of covariance (ANCOVA)
  ➤ Accounts for all available stages of exercise at both time points in all patients
Patient disposition flow chart

N=94 enrolled patients with symptomatic HF + LVEF > 40%

N=44 randomized patients

CONTROL ARM (N=22)

N=22 patients active at 1 month

IASD TREATMENT ARM (N=22)

N=21 patients active at 1 month

N=50 excluded patients:
• MI, PCI, or CABG in past 3 months (n=13)
• Significant untreated CAD (n=11)
• Hx of CVA, TIA, DVT, or PE (n=5)
• Resting RAP > 14 mmHg (n=5)
• Significant valvular disease (n=4)
• Severe CKD (n=2)
• Other (n=10)

N=1 patient withdrew consent after RA could not be accessed (occluded IVC filter)
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<td>Cardiac output (L/min/m²)</td>
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<td>10.9 ± 7.3</td>
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<td>Exercise duration (minutes)</td>
<td>8.9 ± 4.0</td>
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<td>N/A</td>
<td>95.5%</td>
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<td>Total procedure duration (minutes)</td>
<td>12.9 ± 9.0</td>
<td>58.1 ± 25.8</td>
<td>&lt;0.001</td>
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<td>Total fluoroscopy time (minutes)</td>
<td>5.3 ± 3.6</td>
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PRIMARY OUTCOME

RESULTS
## Results: Efficacy outcomes at 1 month

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<td><strong>Primary outcome (exercise PCWP)</strong></td>
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<tr>
<td>• PCWP at 20W (mmHg)* P=0.019</td>
<td>0.9 ± 5.1*</td>
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<td>• PCWP at 40W (mmHg)</td>
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<td>PCWP, peak exercise (mmHg)</td>
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<td>PCWP, workload-corrected (mmHg/W/kg)</td>
<td>10.3 ± 45.9</td>
<td>-5.7 ± 27.3</td>
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<td>RV cardiac output at rest (L/min)</td>
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<td>1.6 ± 1.3</td>
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<td>PVR at rest (Wood units)</td>
<td>0.17 ± 1.57</td>
<td>-0.76 ± 1.59</td>
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<td>PVR during exercise (Wood units)</td>
<td>0.31 ± 1.64</td>
<td>-0.29 ± 1.22</td>
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<td>• PCWP at 60W (mmHg)</td>
<td>-1.3±4.9</td>
<td>-2.3±4.9</td>
<td></td>
</tr>
<tr>
<td><strong>PCWP, legs up at rest (mmHg)</strong></td>
<td>0.0±6.4</td>
<td>-5.0±5.7</td>
<td>0.024</td>
</tr>
<tr>
<td><strong>PCWP, peak exercise (mmHg)</strong></td>
<td>-0.5±5.0</td>
<td>-3.5±6.4</td>
<td>0.144</td>
</tr>
<tr>
<td><strong>PCWP, workload-corrected (mmHg/W/kg)</strong></td>
<td>10.3±45.9</td>
<td>-5.7±27.3</td>
<td>0.231</td>
</tr>
<tr>
<td><strong>RV cardiac output at rest (L/min)</strong></td>
<td>-0.5±1.4</td>
<td>1.6±1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>PVR at rest (Wood units)</strong></td>
<td>0.17±1.57</td>
<td>-0.76±1.59</td>
<td>0.102</td>
</tr>
<tr>
<td><strong>PVR during exercise (Wood units)</strong></td>
<td>0.31±1.64</td>
<td>-0.29±1.22</td>
<td>0.051</td>
</tr>
</tbody>
</table>
Results: Efficacy outcomes at 1 month

<table>
<thead>
<tr>
<th>Hemodynamic parameter</th>
<th>Control</th>
<th>IASD</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome (exercise PCWP)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• PCWP at 20W (mmHg)</td>
<td>0.9 ± 5.1</td>
<td>-3.2 ± 5.2</td>
<td>0.028</td>
</tr>
<tr>
<td>• PCWP at 40W (mmHg)</td>
<td>-1.9 ± 4.3</td>
<td>-1.0 ± 4.5</td>
<td></td>
</tr>
<tr>
<td>• PCWP at 60W (mmHg)</td>
<td>-1.3 ± 4.9</td>
<td>-2.3 ± 4.9</td>
<td></td>
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</tbody>
</table>
Change in PCWP: Baseline to 1 month

**CONTROL**

**IASD**

PCWP (mmHg)

- **Baseline**
- **1 month**

Rest | Legs up | 20W | Peak
---|---|---|---

PCWP (mmHg)

- **Baseline**
- **1 month**

Rest | Legs up | 20W | Peak
---|---|---|---

*P<0.05
**P<0.01
## Results: Safety outcomes at 1 month

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Control (N=22)</th>
<th>IASD (N=22)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACCRE</td>
<td>4.6% (1 renal event)</td>
<td>0%</td>
<td>1.00</td>
</tr>
<tr>
<td>Death</td>
<td>0%</td>
<td>0%</td>
<td>—</td>
</tr>
<tr>
<td>New-onset atrial fibrillation/flutter</td>
<td>0%</td>
<td>0%</td>
<td>—</td>
</tr>
<tr>
<td>Stroke or TIA</td>
<td>0%</td>
<td>0%</td>
<td>—</td>
</tr>
<tr>
<td>Systemic embolization</td>
<td>0%</td>
<td>0%</td>
<td>—</td>
</tr>
<tr>
<td>HF event requiring IV treatment</td>
<td>9.1%</td>
<td>0%</td>
<td>0.49</td>
</tr>
<tr>
<td>Cardiac perforation</td>
<td>0%</td>
<td>0%</td>
<td>—</td>
</tr>
<tr>
<td>Device embolization or occlusion</td>
<td>0%</td>
<td>0%</td>
<td>—</td>
</tr>
<tr>
<td>Major vascular complication</td>
<td>0%</td>
<td>0%</td>
<td>—</td>
</tr>
</tbody>
</table>
Summary

• First RCT of a device-based therapeutic in HfPEF
• REDUCE LAP-HF I trial met its primary endpoint
  ➤ Significantly reduced exercise PCWP at 1 month (P=0.028)
• Good safety profile at 1 month
• Demonstrates beneficial mechanistic effect of IASD
• IASD could have beneficial clinical effects in HfPEF/mrEF
• A larger pivotal trial to examine effects of IASD on QOL, exercise capacity, and clinical outcomes is warranted
• REDUCE LAP-HF II pivotal trial is underway (NCT03088033)
A Transcatheter InterAtrial Shunt Device for the Treatment of Heart Failure with Preserved Ejection Fraction (REDUCE LAP-HF I): A Phase 2, Randomized, Sham-Controlled Trial

Ted Feldman, Laura Mauri, Rami Kahwash, Sheldon Litwin, Mark J. Ricciardi, Pim van der Harst, Martin Penicka, Peter S. Fail, David M. Kaye, Mark C. Petrie, Anupam Basuray, Scott L. Hummel, Rhondalyn Forde-McLean, Christopher D. Nielsen, Scott Lilly, Joseph M. Massaro, Daniel Burkhoff, Sanjiv J. Shah

on behalf of the REDUCE LAP-HF I investigators and research staff

Full study details published today online in Circulation
http://circ.ahajournals.org