Transcatheter Interatrial Shunt for Treatment of Heart Failure

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**Disclosure Statement of Financial Interest**

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

<table>
<thead>
<tr>
<th>Affiliation/Financial Relationship</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grant/Research Support</td>
<td>Abiomed, Ancora, Axon, Edwards,</td>
</tr>
<tr>
<td></td>
<td>Abbott, AquaPass, Axon, BackBeat Medical, BioMind, Corvia, Impulse Dynamics, Therox, Zoll</td>
</tr>
<tr>
<td>Consulting Fees/Honoraria</td>
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<tr>
<td>Ownership/Founder</td>
<td>PVLoops LLC</td>
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</tbody>
</table>
At least 7 Approaches to creating IASD

- Implantable devices:
  - Corvia Atrial Shunt System
  - V-Wave Ventura Shunt
  - Occlutech Atrial Flow Regulator (AFR)
  - Edwards Coronary Sinus Shunt
At least 7 Approaches to creating IASD

- 4 Implantable devices
- 3 that leave no device behind
MODE OF ACTION: Decompression of the left atrium by on-demand shunting from LA → RA (Qp:Qs 1.2-1.3)

Feldman T...Shah SJ. Circ Heart Fail 2016
# Corvia Atrial Shunt Clinical Evidence Development

## Patient Profile:
Symptomatic HF, EF >40%, hemodynamically confirmed elevated LAP

## Pilot Study
*Observational study, 2013*  
(n=11)

**OBJECTIVE**
Evaluate device safety & potential benefit at 30 days.

**RESULTS**
Evidence of significant PCWP drop and procedural safety at 30 days.  
NYHA & QoL improvements at 1 year.

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## REDUCE LAP-HF
*Observational study, 2015*  
(n=64)

**OBJECTIVE**
Understand device safety & therapy performance in larger patient cohort.

**RESULTS**
Evidence of sustained PCWP drop and device patency at 6m & 12m.  
Sustained symptom, 6MWT, QoL improvement through 3 years.

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## REDUCE LAP-HF I
*Randomized, blinded, sham-controlled trial, 2016*  
(n=44)

**OBJECTIVE**
Evaluate peri-procedural safety & device effectiveness against control arm.

**RESULTS**
Demonstrated mechanistic effect. Improvement in HF events, QoL, and symptoms vs. control at 1 year.  
100% shunt patency at 1 year.

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## REDUCE LAP-HF II
*Randomized, blinded, sham-controlled trial, 2020*  
(n=626)

**OBJECTIVE**
Evaluate safety & clinical efficacy against control arm in powered study.

**RESULTS**
Overall neutral; safety consistent with prior studies; large responder population with improvement of QoL and reduction of HF events.

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1. Malek et al. *Int J Cardiol*, 2015;  
5. Unpublished 3-year results on file at Corvia Medical;  
7. Shah SJ et al. *JAMA Cardiol*, 2018;  
REDUCE LAP-HF II study design\textsuperscript{1}

**PHASE III, MULTI-CENTER, DOUBLE-BLIND, SHAM-CONTROLLED TRIAL**

**PURPOSE:** Evaluate the clinical efficacy and safety of the Corvia Atrial Shunt to improve quality of life and reduce HF related symptoms and events in patients with HFpEF or HFmrEF

**Study Population**
- N = 626 randomized
- Symptomatic HF, ongoing GDMT, age ≥40, LVEF ≥40%, preserved RV function, elevated exercise PCWP (≥25 mm Hg) with left-to-right gradient (≥ 5mmHg)

**Atrial Shunt Treatment**
- N=314

**Sham Control**
- NN=312

**PRIMARY ENDPOINT**
Hierarchical composite of cardiovascular mortality or non-fatal, ischemic stroke through 12m, rate of total HF events (first and recurrent) through 24m & time to first HF event, change in KCCQ score between baseline & 12m

**SECONDARY ENDPOINTS**
- Composite safety endpoint (MACCRE)
- Rate of HF admissions or IV diuresis, through 24m
- Change in NYHA Class between baseline & 12m
- Change in KCCQ score between baseline & 12m

\textsuperscript{1}Berry, N et al. *Am Heart J*, vol. 226 (2020): 222-231
## REDUCE LAP-HF II Primary Results

### Primary Endpoint Win Ratio* (95% CI) p-Value

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Win Ratio* (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite Endpoint</td>
<td>0.98 (0.8, 1.2)</td>
<td>0.85</td>
</tr>
</tbody>
</table>

### Efficacy Endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Treatment (N = 309)</th>
<th>Control (N = 312)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death or non-fatal ischemic stroke</td>
<td>1% (4 events)</td>
<td>1% (2 events)</td>
<td>0.41</td>
</tr>
<tr>
<td>Cardiovascular Death</td>
<td>1% (4 events)</td>
<td>1% (2 events)</td>
<td>0.65</td>
</tr>
<tr>
<td>Non-fatal Ischemic Stroke</td>
<td>&lt;1% (1 event)</td>
<td>0% (0 events)</td>
<td>0.32</td>
</tr>
<tr>
<td>Total HF events per patient-year</td>
<td>0.28</td>
<td>0.25</td>
<td>0.45</td>
</tr>
<tr>
<td>Change in KCCQ-OSS (Mean ± SD)</td>
<td>11.5±22</td>
<td>10.5±21</td>
<td>0.73</td>
</tr>
<tr>
<td>Change in NYHA Class</td>
<td>-0.5 (-1.0, 0.0)</td>
<td>0.0 (-1.0, 0.0)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

*In win ratio calculation, all patients are compared with each other in pairwise manner on values of the components in a hierarchical manner (1 = neutral, >1 = treatment better, <1 = sham better)
High Exercise PVR + Pacemaker: Key Factors in Clinical Outcomes

SYSTEMATIC STATISTICAL ANALYSIS IDENTIFIED MOST SIGNIFICANT VARIABLES AFFECTING HF EVENT RATE

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>( P_{interaction} )</th>
<th>HF event IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peak Exercise PVR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&lt;1.74) WU(^1)</td>
<td>0.031</td>
<td>0.71 (0.42, 1.20)</td>
</tr>
<tr>
<td>(N=382)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\geq1.74) WU (N=191)</td>
<td></td>
<td>2.48 (1.23, 5.01)</td>
</tr>
<tr>
<td><strong>Pacemaker(^2)</strong></td>
<td>0.049</td>
<td></td>
</tr>
<tr>
<td>No PM (N=523)</td>
<td></td>
<td>1.05 (0.67, 1.65)</td>
</tr>
<tr>
<td>Yes PM (N=103)</td>
<td></td>
<td>3.12 (1.21, 8.05)</td>
</tr>
</tbody>
</table>

High exercise pulmonary vascular resistance (PVR) and presence of a pacemaker result in a 2-3 x increased risk of HF events

\(^1\)Upper tertile, which roughly corresponds to peak exercise in a healthy adult > 55 years (≤1.8WU); \(^2\)Includes CRT
The Responder Group shows significant improvement over sham control in Win ratio, HF event IRR, and KCCQ-OSS.
Patients with high exercise PVR and Pacemakers in this study had common comorbidities:

- worse RV strain
- lower TAPSE
- larger RA
  and/or
- more TR
**Primary Endpoint Responder Group**

**Patients with normal exercise PVR and no pacemaker derive significant HF and QOL benefit**

<table>
<thead>
<tr>
<th>Responder Group</th>
<th>Variable</th>
<th>Treatment (N=161)</th>
<th>Sham Control (N=152)</th>
<th>Win Ratio</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak PVR &lt; 1.74 no pacemaker</td>
<td>Composite Endpoint (KCCQ Threshold=5)</td>
<td></td>
<td></td>
<td>1.5</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>CV death or non-fatal ischemic stroke</td>
<td>1.24% (2 events)</td>
<td>0% (0 events)</td>
<td>-</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>Total HF events per patient-year</td>
<td>0.12</td>
<td>0.22</td>
<td>-</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>Change in KCCQ-OSS (Mean ± SD)</td>
<td>15.5 ± 22.2 (153)</td>
<td>10.0 ± 20.6 (141)</td>
<td>-</td>
<td>0.01</td>
</tr>
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</table>
Significant reduction in total HF events for treated patients.

HF event curves for shunt therapy and sham control arms begin to separate around 3 months.

P-value = 0.0751

TREATMENT: At risk 161 160 160 160 117 103 95 85
CONTROL: At risk 152 152 150 150 101 86 83 75

1 Up to 24 months follow-up
REDUCE LAP-HF II is the largest interventional device therapy trial (n=626) in HFpEF, the largest unmet need in cardiology.

The study has significantly advanced the understanding of patient selection, and we have established criteria that identify a responder group, which represent >50% of the trial population.

Patients with normal exercise pulmonary vascular resistance (PVR <1.74) and without a pacemaker derived significant clinical benefit from the shunt:
- 45% reduction in the rate of HF events (0.12 vs. 0.22 events per patient-year, p = 0.007)
- 55% greater improvement in health status over sham (+5.5 points, p = 0.01) as assessed by KCCQ overall summary score, including 40% more patients with a very large (>20 points) quality of life improvement

There is biological plausibility for the criteria defining the subgroup and is further supported by congruence in clinical outcomes, including a reduction in the HF event rate and an improvement in health status (both KCCQ and NYHA class).

Exercise hemodynamic phenotyping played a critical role in defining the responder group.