Late Breaking Clinical Trials II
REDUCE LAP-HF II

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German Center for Cardiovascular Research
On behalf of the Steering Committee, Investigators and Research Staff
Conflicts of interest

- Servier: Honorarium for presentations, Consultant
- Boehringer: Consultant
- Impulse Dynamics: Consultant, Honorarium for presentations
- Novartis: Consultant, Honorarium for presentations
- Pfizer: Honorarium for presentations
- AstraZeneca: Honorarium for presentations, Consultant
- Bayer: Honorarium for presentations
- Corvia: Consultant, no honorarium
- Vifor: Honorarium for presentations
High LA pressures impact QOL & survival

During exercise, HFpEF patients experience a significant rise in PCWP compared to control

As PCWP rises, patient exercise capacity falls

Corvia Atrial Shunt: 8mm Qp:Qs 1.27
Shunt allows blood to move from the higher pressure LA to the lower pressure more compliant right side, reducing LAP and pulmonary venous hypertension

Borlaug et al. Circ Heart Fail 2010
Wolsk et al. Eur J Heart Fail 2017
**REDUCE LAP-HF II – Study design**

**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 rest (>15 mmHg) or exercise PCWP (≥25 mmHg) with left-to-right gradient (≥5 mmHg)

**Atrial Shunt Treatment**  
n=314

**Sham Control**  
n=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

*Berry et al. Am Heart J 2020*

*Shah et al. Lancet 2022*
## REDUCE LAP-HF II – Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Atrial shunt device (n=314)</th>
<th>Sham procedure (n=312)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>73</td>
<td>72</td>
</tr>
<tr>
<td>Female</td>
<td>64%</td>
<td>59%</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>31.6</td>
<td>32.2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>89%</td>
<td>87%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>37%</td>
<td>37%</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>50%</td>
<td>53%</td>
</tr>
<tr>
<td>NYHA class III</td>
<td>77%</td>
<td>78%</td>
</tr>
<tr>
<td>HF hospitalization in last 12 mo.</td>
<td>26%</td>
<td>32%</td>
</tr>
<tr>
<td>NTproBNP, pg/ml (sinus rhythm)</td>
<td>301</td>
<td>344</td>
</tr>
<tr>
<td>NTproBNP, pg/ml (atrial fibrillation/flutter)</td>
<td>1008</td>
<td>1230</td>
</tr>
<tr>
<td>KCCQ-OSS</td>
<td>46</td>
<td>45</td>
</tr>
<tr>
<td>HFpEF (EF ≥50%)</td>
<td>93%</td>
<td>93%</td>
</tr>
</tbody>
</table>

Median values shown for all continuous variables
### REDUCE LAP-HF II – Baseline medications

<table>
<thead>
<tr>
<th>Medications</th>
<th>Atrial shunt device (n=314)</th>
<th>Sham procedure (n=312)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loop diuretics</td>
<td>83%</td>
<td>81%</td>
</tr>
<tr>
<td>MRAs</td>
<td>53%</td>
<td>51%</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>2%</td>
<td>4%</td>
</tr>
<tr>
<td>Sacubitril/valsartan</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>24%</td>
<td>25%</td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
<td>39%</td>
<td>37%</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>70%</td>
<td>70%</td>
</tr>
<tr>
<td>Oral anticoagulants</td>
<td>47%</td>
<td>52%</td>
</tr>
<tr>
<td>Aspirin</td>
<td>37%</td>
<td>40%</td>
</tr>
<tr>
<td>Other anti-platelet therapy</td>
<td>11%</td>
<td>12%</td>
</tr>
</tbody>
</table>
REDUCE LAP-HF II – Primary composite endpoint

Cumulative incidence of CVD death or CVA (%)

- Atrial shunt device
- Sham procedure

Log-rank P=0.42

Cumulative incidence of HF events (%)

- Atrial shunt device
- Sham procedure

Log-rank P=0.41

- Finkelstein-Schoenfeld p-value=0.85
- Win ratio: 1.0 (95% 0.8-1.2)
### REDUCE LAP-HF II – Primary results

<table>
<thead>
<tr>
<th>Primary 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>

<table>
<thead>
<tr>
<th>Efficacy Endpoints</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% (3 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 (Median (IQR))</td>
<td>10.2 (-1.8-26.8)</td>
<td>9.4 (-2.1-22.9)</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)

Shah et al. Lancet 2022
## REDUCE LAP-HF II – Safety endpoints

<table>
<thead>
<tr>
<th>Safety endpoint</th>
<th>Atrial shunt device (n=309)</th>
<th>Sham procedure (n=312)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite safety endpoint</td>
<td>38%</td>
<td>31%</td>
<td>0.11</td>
</tr>
<tr>
<td>New-onset worsening renal function</td>
<td>7%</td>
<td>8%</td>
<td>0.66</td>
</tr>
<tr>
<td>Major cardiac events</td>
<td>4%</td>
<td>1%</td>
<td>0.025</td>
</tr>
<tr>
<td>• Cardiac death</td>
<td>1%</td>
<td>1%</td>
<td>1.00</td>
</tr>
<tr>
<td>• Myocardial infarction</td>
<td>2%</td>
<td>&lt;1%</td>
<td>0.14</td>
</tr>
<tr>
<td>• Cardiac tamponade</td>
<td>1%</td>
<td>0%</td>
<td>0.95</td>
</tr>
<tr>
<td>• Emergency cardiac surgery</td>
<td>&lt;1%</td>
<td>0%</td>
<td>0.96</td>
</tr>
<tr>
<td>Embolic complications</td>
<td>0%</td>
<td>0%</td>
<td>—</td>
</tr>
<tr>
<td>Newly acquired atrial fibrillation/flutter</td>
<td>1%</td>
<td>1%</td>
<td>0.42</td>
</tr>
<tr>
<td>≥30% ↑RV size or ≥30% ↓TAPSE</td>
<td>30%</td>
<td>25%</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Modified intention-to-treat population (excludes 5 patients who did not receive shunt device in active treatment arm)
REDUCE LAP-HF II – Pre-specified subgroup analyses
Recurrent HF events

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>IRR (95% CI)</th>
<th>P_{interaction}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Male</td>
<td>239</td>
<td>1.32 (1.01-1.71)</td>
<td>0.020</td>
</tr>
<tr>
<td>• Female</td>
<td>382</td>
<td>0.85 (0.55-1.09)</td>
<td></td>
</tr>
<tr>
<td><strong>RA volume index</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Tertile 1</td>
<td>167</td>
<td>0.79 (0.57-1.11)</td>
<td>0.012</td>
</tr>
<tr>
<td>• Tertile 2</td>
<td>168</td>
<td>0.70 (0.46-1.07)</td>
<td></td>
</tr>
<tr>
<td>• Tertile 3</td>
<td>168</td>
<td>1.43 (1.08-1.90)</td>
<td></td>
</tr>
<tr>
<td><strong>PA systolic pressure at 20W</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Tertile 1</td>
<td>192</td>
<td>0.71 (0.46-1.11)</td>
<td>0.002</td>
</tr>
<tr>
<td>• Tertile 2</td>
<td>202</td>
<td>0.80 (0.57-1.12)</td>
<td></td>
</tr>
<tr>
<td>• Tertile 3</td>
<td>202</td>
<td>1.40 (1.10-1.79)</td>
<td></td>
</tr>
</tbody>
</table>

Statistical significance threshold: interaction p-value <0.05
High peak PVR + pacemakers: Key factors in trial outcome
Systematic statistical analysis identified most significant variables affecting clinical efficacy

Prespecified Subgroup Analysis

Factors that Affect PA Pressure

PAs pressure = PCWP+ (CO x PVR)

- Identified exercise PVR as having the most impact on clinical efficacy
  - With low exercise PVR (peak <1.74), win ratio 1.31
  - With high exercise PVR (peak ≥1.74 WU), win ratio 0.60

2 subtypes of HFpEF: PVR ↓ PVR ↑

- Presence of a pacemaker result in a 3x increased risk of HF events

Responder group
Borlaug et al. Circulation 2022 (in press)
Primary endpoint in Responder group
Patients with normal exercise PVR (<1.74 WU) and no pacemaker derive significant HFH and QoL benefit

<table>
<thead>
<tr>
<th>Subgroup</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>0.004</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 100 patient-years</td>
<td>12</td>
<td>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>0.027</td>
</tr>
</tbody>
</table>

OVERALL COHORT (n=626)
RESPONDER GROUP (n=313)
Exclude high ex PVR and pacemaker (50% of patients)

Borlaug et al. Circulation 2022 (in press)
**Summary**

**REDUCE LAP-HF II is the largest device therapy trial in HFpEF**
- Placement of atrial shunt device did not reduce total rate of HF events or improve health status overall in HF with EF ≥40%.
- Subgroup analyses suggests a potential responder group.

  *Shah et al. Lancet 2022*

- 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
  - 55% greater improvement in KCCQ-OSS over sham including 40% more patients with >20 points improvement of KCCQ-OSS

  *Borlaug et al. Circulation 2022 (in press)*

- A confirmatory randomized trial is under review by FDA
  - HFpEF, $PCWP_{Ex} \geq 25$ mmHg, LA/RA gradient $\geq 5$mmHg, $PVR_{Ex} < 1.75$ WU, no Cardiac Rhythm Device
Thank you!

Patients
Site investigators
Committee members